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Executive Summary

for the Obstetrics and Gynecology Devices Panel of FDA's Medical Devices Advisory Committee, February 12, 2019

Regarding the Treatment of
Anterior Pelvic Organ Prolapse with
Transvaginal Surgical Mesh

Available for Public Disclosure without Redaction

This document is an Executive Summary of Coloplast's experience regarding the use of surgical mesh for the treatment of anterior pelvic organ prolapse prepared for the Food and Drug Administration Meeting of the Obstetrics and Gynecology Devices Panel on February 12, 2019 to Discuss the Benefits and Risks of Transvaginal Surgical Mesh Used in the Treatment of Anterior Pelvic Organ Prolapse

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2. ABBREVIATIONS

Abbreviation	Term
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
AUGS	American Urogynecologic Society
CEC	Clinical Events Committee
C.F.R.	Code of Federal Regulations
HHS	The Department of Health and Human Services
FDA	Food and Drug Administration
FDA's DEPI/OSB	FDA's Division of Epidemiology (DEPI)/Office of Surveillance and Biometrics (OSB)
FDCA	Food, Drug, and Cosmetic Act (21 US Code Chapter 9)
Fed. Reg.	Federal Register
MDR	Medical Device Report
mITT	Modified Intent to Treat
Mpathy	Mpathy Medical Inc.
NTR	Native Tissue Repair
OB-GYN Panel	Obstetrics and Gynecology Devices Panel of Medical Devices Advisory Committee
Panel	The February 12, 2019 Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee
PFDI-20	Pelvic Floor Distress Inventory
PFDR	Pelvic Floor Disorders Registry
PFIQ-7	Pelvic Floor Impact Questionnaire
PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire
PI	Principal Investigator
PMA	Premarket Approval
POP	Pelvic Organ Prolapse
POP-Q	Pelvic Organ Prolapse Quantification (System)
POPDI-6	POP Distress Inventory 6
Restorelle 522 Study	The Section 522 Study Conducted by Coloplast for Restorelle DirectFix Anterior Mesh, "Restorelle® Transvaginal Mesh versus Native Tissue Repair for Treatment of Pelvic Organ Prolapse 522 Study"
SAE	Serious Adverse Event
522 Study	A Postmarket Surveillance Study Mandated by FDA under Section 522 of the FDCA
SUI	Stress Urinary Incontinence
TVL	Total Vaginal Length

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3. INTRODUCTION

3.1 Purpose of the Panel Meeting

The Food and Drug Administration (FDA) has convened the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee (the Panel) to receive the Panel's "scientific and clinical input on assessing the effectiveness, safety, and benefit/risk of mesh placed transvaginally in the anterior vaginal compartment, as well as identifying the appropriate patient population and physician training needed for these devices."[1]

Thus, the Panel is asked to provide input on the factors that FDA should consider when it assesses the effectiveness, safety, and benefit/risk of the use of surgical mesh placed transvaginally for the treatment of anterior pelvic organ prolapse (POP), and the appropriate patient population and surgeon training. The Panel's advice is timely because this meeting is being held during the ongoing review of Premarket Approval (PMA) applications submitted to FDA, including one by Coloplast Corp. (Coloplast), for transvaginal mesh medical devices for anterior POP repair.

This document is intended to provide the Panel members with knowledge of the postmarket experience of Coloplast through the long history of use in the United States for the Restorelle DirectFix Anterior mesh. The information in specific sections of this document may be informative to the Panel in advising FDA on the factors it should consider, including:

- The design characteristics of the mesh device;
- The distinctive design features and characteristics of the patients who are enrolled in the Restorelle 522 Study, one of the real-world postmarket surveillance studies ("522 study") that was ordered by FDA and that provide the key clinical study data for the Coloplast PMA submission under FDA review. In particular, the non-randomized design and use of pre-enrollment surgeon and patient consultation and discussion to choose the treatment group (as opposed to random assignment) are key aspects of the study design;
- Contemporary understanding of the potential risks of use of surgical mesh for anterior POP surgery and how thoroughly these risks are understood;
- The characteristics of the patients with anterior POP who require surgical repair, including the prior surgical history and clinical factors that may indicate the need for a transvaginal approach and additional mechanical support during the repair and healing process;

[1] Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments, 83 Fed. Reg. 63,516 (Dec. 10, 2018).

- The impact of the surgeon's knowledge of patient anatomy and surgical skill and ability to deliver appropriate patient counseling, patient selection, surgical technique, and identification and management of complications; and

- Whether surgeons need the option of transvaginal surgical mesh for the treatment of anterior POP for certain patients.

3.2 Clinical Condition: Overview of Anterior POP

POP is defined as a protrusion of the pelvic organs into or out of the vaginal canal. POP occurs when the internal structures that support the pelvic organs such as the bladder, uterus, bowel, or rectum, become weak or stretched such that the organs drop from their normal position and bulge (prolapse) into the vagina.[2,3] Depending on the organs and anatomical sites involved, different types of vaginal wall prolapse can occur. These include anterior vaginal wall prolapse, prolapse of the apex (which includes vaginal vault and uterine prolapse in the apical position), and posterior vaginal wall prolapse. A woman can have prolapse of one or more of these vaginal compartments and the condition usually progresses over time.

Anterior POP—the focus of this Panel, and also known as cystocele, vaginal prolapse, or prolapsed (dropped) bladder—occurs when the supportive tissue between a woman's bladder and vaginal wall weakens and stretches, allowing the bladder to bulge into the vagina. It is this condition, and the associated transvaginal surgical treatment, that is the main subject of this document and this Panel meeting.

While most commonly not a life-threatening condition, women with POP often experience pelvic discomfort; disruption of their sexual, urinary, and defecatory functions; and an overall reduction in their quality of life.[4] Common symptoms include pelvic heaviness; bulge, lump, or protrusion coming down from the vagina; a dragging sensation in the vagina; or backache. These symptoms may gradually worsen over time causing more severe symptoms. Symptoms of bladder, bowel, or sexual dysfunction are frequently present.

Normal anatomy and typical presentation of the different POP pathologies are shown in **Figure 3-1**. The condition treated by anterior POP repair, cystocele, is depicted in the bottom left of the image and the condition treated by apical POP repair, uterine prolapse, is depicted in the top right of the image.

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[2] Haylen BT, Maher CF, Barber MD, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). *Int Urogynecol J* 2016;27:165-94.

[3] Abrams P, Cardozo L, Wagg A, Wein A. Incontinence. 6th ed. Bristol, UK: ICI-ICS. International Continence Society, 2017;ISBN: 978-0-956960733, at 61.

[4] Sentilhes L, Berthier A, Sergent F, Verspyck E, Descamps P, Marpeau L. Sexual function in women before and after transvaginal mesh repair for pelvic organ prolapse. *Int Urogynecol J* 2008;19:763-72.

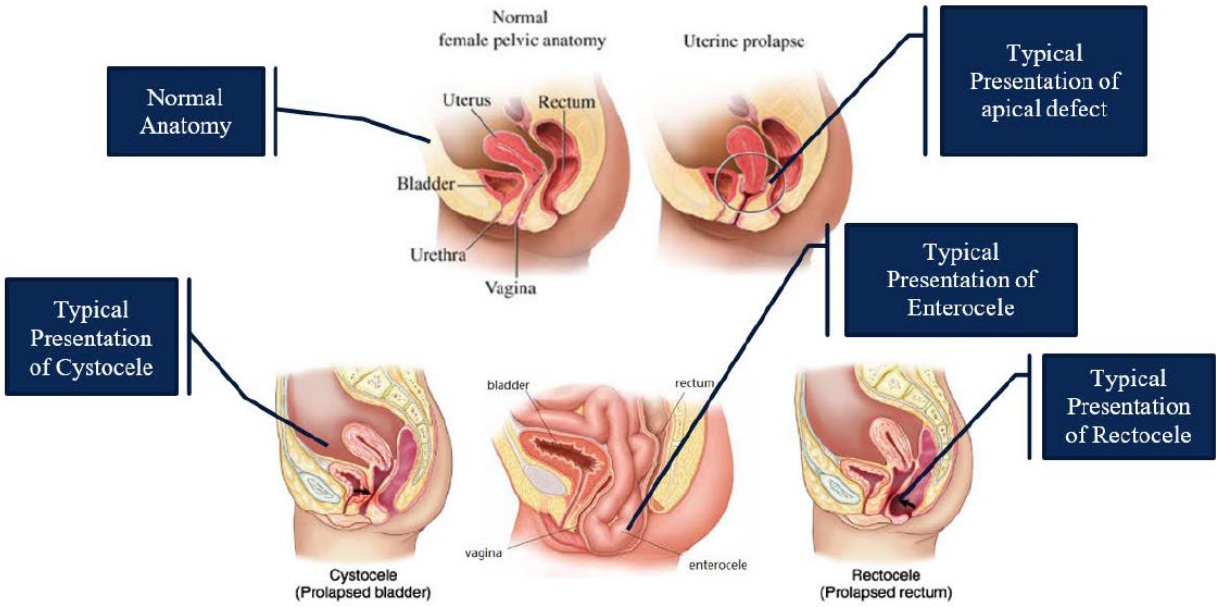

Figure 3-1. Disease States

3.3 Current Medical and Surgical Options

For anterior POP, conservative management such as lifestyle changes, physical therapy, or vaginal pessaries are generally considered for women with mild symptoms or those women who do not want surgery or are poor surgical candidates. When conservative measures fail to provide adequate symptom relief, surgical correction may be indicated.

A variety of reconstructive procedures are available for women who are considered viable surgical candidates. Reconstructive procedures may use the patient's native tissue, or the procedure may be augmented through use of biological or synthetic materials such as allografts (*e.g.*, cadaveric fascia), xenografts (*e.g.*, porcine and bovine), autografts (*e.g.*, fascia lata and rectus fascia), and synthetic meshes. The surgical route for repair may be vaginal or abdominal (laparoscopic/robot-assisted). The choice of the interventional procedure depends on several factors, including: the patient's goals, the nature, site, and severity of the prolapse; whether there are additional symptoms affecting urinary, bowel, or sexual function; the general health and surgical history of the woman; and surgeon experience.

Importantly, as discussed below the transvaginal use of surgical mesh is an appropriate surgical treatment option for certain women in pelvic reconstructive surgery seeking to treat anterior POP.

3.4 Patients and Surgeons Need Options

Although some patients can be adequately treated with native tissue or abdominal graft repairs for anterior vaginal prolapse, other patients may be poor candidates for these types of procedures for various reasons and may benefit from transvaginal POP repair with surgical mesh.

- Native tissue repair is not a good option for many patients for whom a surgical assessment has determined that poor tissue may result in inadequate support if using native tissue alone; and

- Abdominal surgeries are not good options for many patients with general anesthesia intolerance, morbid obesity, multiple prior abdominal procedures, risk of trocar or abdominal hernia formation, risk of bowel obstruction, or inability to tolerate a Trendelenburg position.

In these kinds of clinical situations, surgical mesh, such as the Restorelle DirectFix Anterior mesh, provides an option to allow for a single-incision transvaginal approach to address anterior vaginal prolapse and to use surgical mech to provide additional anatomic support.

3.5 Current Indication and Regulatory Status for Restorelle DirectFix Anterior Mesh

The Restorelle DirectFix Anterior mesh and other models of Restorelle surgical mesh are currently marketed in the United States under 510(k) K103568, with the following indication for use:

> Restorelle polypropylene mesh may be used for the repair of abdominal wall hernia, including inguinal, femoral, and incisional, and uterovaginal prolapse and other fascial deficiencies that require support material. It may be used in open or laparoscopic abdominal procedures or for repair by the vaginal route.

The Restorelle surgical mesh was developed by a urogynecologist with specific consideration for use for with treatment for vaginal prolapse. Restorelle DirectFix Anterior was developed specifically for transvaginal treatment of anterior POP.

On January 3, 2012, FDA ordered manufacturers of surgical mesh for transvaginal repair of POP to conduct prospective postmarket surveillance studies under the authority of Section 522 of the Federal Food, Drug and Cosmetic Act (FDCA). This postmarket surveillance program has provided rigorous and continuous oversight by FDA's Division of Epidemiology (DEPI)/Office of Surveillance and Biometrics (OSB) of the study of our medical device.

Final orders regarding re-classification for surgical mesh medical devices used for transvaginal POP repair and requirements for filing PMA applications were issued by FDA on January 5, 2016. In FDA's final order requiring PMA applications following reclassification of surgical mesh for transvaginal POP repair into Class III, the Agency stated that by "requiring PMA approval, FDA can require an independent demonstration that a reasonable assurance of safety and effectiveness exists for each device within this type."[5] FDA's final order also provided FDA's expectation that patient labeling contain relevant benefit/risk information, namely, that "patient labeling should include relevant information from FDA's Safety Communication and/or FDA's Urogynecologic Surgical Mesh Implants Web page . . . [and] include a link to the FDA's

[5] Obstetrical and Gynecological Devices; Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair; Final Rule, 81 Fed. Reg. 363 (Jan. 5, 2016).

Urogynecologic Surgical Mesh Implants Web page."[6] In response to comments received by FDA on the proposed PMA order and that were calling for the ban, recall, or suspension of use of surgical mesh devices, the Agency also stated:

> FDA has determined that the safety and effectiveness of surgical mesh for transvaginal POP repair has not been established and that the collection of additional clinical evidence on these devices is needed. Such additional evidence may provide information to allow FDA to impose controls to mitigate the risks and more clearly characterize the benefits of these devices. In addition, **FDA believes there are potential benefits from surgical mesh used for transvaginal POP repair including treatment of POP in appropriately selected women with severe or recurrent prolapse**. As such, FDA has not determined that this device presents 'an unreasonable and substantial risk of illness or injury.'[7] (Emphasis added)

Importantly, FDA also determined that the 12-month data from the postmarket Restorelle 522 Study should be submitted to support PMA applications, with an additional two to four years of follow-up data.[8]

In conjunction with these orders, Coloplast has submitted a PMA application for Restorelle DirectFix Anterior mesh for the treatment of anterior POP and it is currently under review by FDA. The outcome data and statistical analyses found in the PMA applications are not the subject of this Panel.

The Restorelle DirectFix Anterior mesh is one of only three surgical mesh medical devices currently available in the United States for treatment of anterior POP. The regulatory history is described in more detail in Section 5.

3.6 Summary Statement

Transvaginal surgical mesh for anterior POP repair—like Restorelle DirectFix Anterior mesh—is a safe, effective, and important treatment option for many surgeons who treat women diagnosed with anterior POP. Transvaginal treatment with surgical mesh should remain available as an option for those surgeons who have patients for which the surgeon has determined that the potential benefits of transvaginal anterior POP repair with surgical mesh are likely to outweigh any potential risks. Factors that the Panel may find relevant in consideration of surgical mesh medical devices for transvaginal anterior POP repair, and for which the company's postmarket experience may provide helpful insights, include:

- Key technical features of surgical mesh, including its design and characteristics as a polypropylene monofilament, ultra-lightweight, and Type 1 macroporous mesh, that optimize its efficacy and safety for transvaginal anterior POP repair. The design and

[6] Obstetrical and Gynecological Devices; Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair; Final Rule, 81 Fed. Reg. 363 (Jan. 5, 2016).

[7] Obstetrical and Gynecological Devices; Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair; Final Rule, 81 Fed. Reg. 354, 355 (Jan. 5, 2016).

[8] Obstetrical and Gynecological Devices; Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair Final Rule, 81 Fed. Reg. 354 (Jan. 5, 2016).

characteristics of Restorelle DirectFix Anterior mesh are described in Section 4 of this document.

- The regulatory history that includes an extensive history of postmarket experience for Coloplast's transvaginal anterior mesh. Based on the 2012 FDA requirement for 522 studies, the regulatory history also includes rigorous FDA oversight of the postmarket study of the Restorelle surgical mesh. The regulatory history of Restorelle DirectFix Anterior mesh is briefly summarized in Section 5.

- The distinctive real-world design of the Restorelle 522 Study that compares the efficacy and safety of surgical mesh versus native tissue repair for anterior POP. This study was mandated by FDA and its design and protocol were approved by FDA. The study's 12-month results in the PMA application are currently under review by FDA. Key considerations are: (1) the study is not a randomized study; (2) its study design mandates pre-enrollment consultation and discussion between the patient and the surgeon regarding the choice to participate in the surgical mesh cohort or native tissue repair cohort for anterior POP repair; and (3) surgical expertise and patient characteristics affect outcomes.

  Thus, it is important that the Panel consider factors that may help FDA to evaluate clinical data from a real-world, two-cohort postmarket surveillance study in which subjects were not randomized to the use of surgical mesh or native tissue repair. The design of the Restorelle 522 Study is presented in Section 6. The ways in which the pre-enrollment consultation and discussion between the patient and the surgeon to choose the treatment group (as opposed to random assignment) may have affected the distribution of the baseline characteristics of subjects across the surgical mesh and native tissue repair treatment arms is presented in Section 7.

- Analyses of: (1) postmarket safety data and Medical Device Reports (MDRs); and (2) the scientific and medical literature. Surgical mesh medical devices are not new devices for which there is no available postmarket safety information. Surgical mesh medical devices used in the transvaginal anterior POP treatment have been cleared by FDA for use for more than a decade, resulting in a long history of postmarket safety information. The postmarket safety data for Restorelle mesh used for the transvaginal treatment of anterior POP are discussed in detail in Section 8 of this document and a review of the contemporary literature applicable to surgical mesh medical devices used in the transvaginal repair of anterior POP that have the same characteristics as Restorelle DirectFix Anterior mesh is presented in Section 9.

- In its recommendations to FDA regarding factors the Agency should consider regarding the appropriate population for the use of surgical mesh in transvaginal repair of anterior POP, the Panel may consider whether there exists a population of women for whom these devices are an appropriate option. Information regarding Coloplast's understanding of the contemporary patient population in the United States for which transvaginal anterior POP repair with surgical mesh is prescribed is addressed in Section 10 and Section 12 of this document.

- In its recommendations to FDA, the Panel should also consider appropriate surgeon skills and education regarding patient selection, surgical device placement, and the identification and management of adverse events (AE) to optimize the benefit for the appropriate patient population and to mitigate the potential for the occurrence and severity of potential clinical risks known to be associated with anterior POP repair. Additionally, and fundamental to a treatment decision, surgeon education can ensure a robust discussion between the surgeon and patient, which results in an informed treatment decision. Information regarding surgeon education and training considerations on transvaginal anterior POP repair is addressed in Section 11 of this document.

Coloplast appreciates the opportunity to present its position, postmarket experiences, and views to the Panel, and hopes that the discussion, as well as the information in this document, will be informative and helpful for the Panel's deliberations regarding the factors that FDA should consider when evaluating the efficacy, safety, and benefit/risk profile of transvaginal surgical mesh for anterior POP repair, as well as the appropriate population and surgeon training.

4. DEVICE DESCRIPTION AND CHARACTERISTICS

4.1 Focus of this Section

This section is provided so that the Panel members may benefit from understanding Coloplast's experience regarding how key properties, characteristics, and operational features of Restorelle DirectFix Anterior mesh may contribute to the device's performance and safety profile. Coloplast hopes this information will be informative and helpful as the Panel considers how mesh design may be a factor that FDA should consider in its assessment of the efficacy, safety, and benefit/risk profile of surgical mesh medical devices intended for transvaginal repair of anterior POP.

4.2 Overview

Restorelle DirectFix Anterior mesh is a permanent, macroporous, synthetic implant knitted of medical grade, non-absorbable, monofilament 100% polypropylene. There are no color additives in this device. It is intended as a permanent mesh implant for anterior POP treatment and it is designed to be placed on the anterior side of the vagina between the vagina and the bladder. It is implanted using a transvaginal route to function as a mechanical scaffold and to provide mechanical support or bridging material for defects in the supportive tissues of the vagina.

The device's construction utilizes a warp-knit process resulting in a mesh fabric that can be cut into any desired shape or size without unraveling (lock-knit). This feature provides the surgeon with the option to cut and tailor the mesh to treat a patient's specific fascial deficiencies; however, the Restorelle DirectFix Anterior mesh is offered in a standard shape so that there is little to no additional intraoperative tailoring needed. The device is supplied as a sterile, single-use finished medical device.

It is important to appreciate that not all synthetic mesh medical devices are the same. Restorelle DirectFix Anterior mesh is an ultra-lightweight, Type 1 mesh (per the Amid classification system for biomaterials) with monofilament polypropylene fibers that are weaved into a macroporous (>75 µm) architecture. In FDA's consideration of factors that may influence the performance of synthetic surgical mesh medical devices in the treatment of POP, the Agency observed that lightweight and Type 1 mesh medical devices may reduce the inflammatory response and enhance mesh performance in comparison to other types of mesh:

> *The synthetic materials are supplied as either monofilament or multifilament fibers that are weaved into the mesh form. Typically, these fibers are weaved to create a porous architecture to reduce inflammatory tissue response to the mesh following implantation. In addition to the fiber type and weave, other factors such as the thickness of the fibers, the density and strength of the material, the implantation technique, and the biological and physical responses of the surrounding tissue influence the performance of the mesh.*
>
> *Another means to reduce the inflammatory response and potentially enhance mesh performance is to manufacture lightweight, Type I (Amid classification) mesh. Type I mesh products are composed of monofilament fibers that are weaved into a macroporous (>75 µm) architecture. The design of these types*

of mesh products promotes better integration into the host tissue through the formation of a scar net rather than a scar plate during the foreign body response.[9] (Emphasis added)

For a surgical mesh to perform as intended, specific polypropylene mesh attributes, such as material, geometry, porosity, conformability, and thickness, must be optimized. Each of these attributes of Restorelle DirectFix Anterior mesh is discussed in more detail in Section 4.4.

4.3 Illustration of the Device

Restorelle DirectFix Anterior mesh is flat with four arms; two long proximal arms and two short distal arms (**Figure 4-1**). The long, proximal arms of the device contain a denser knit pattern that provide visual and tactile reference for proper orientation of the device upon implantation. The proximal arms visually identify which location of the device is used for fixation to the sacrospinous ligament.

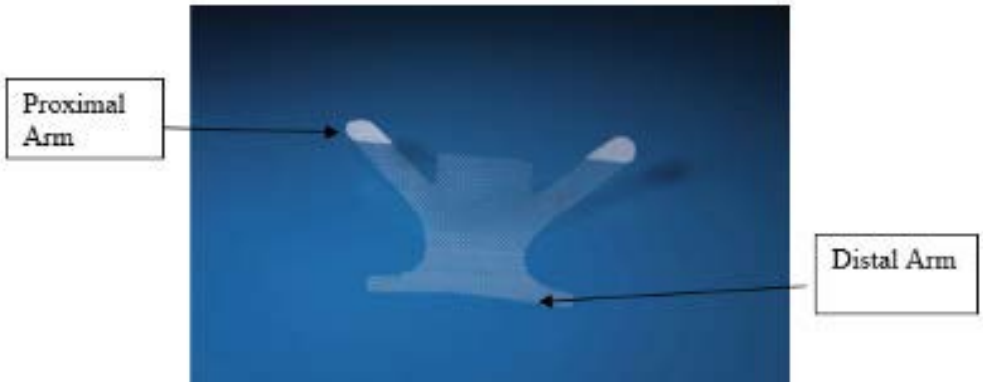

Figure 4-1. Restorelle DirectFix Anterior Mesh

The warp knit structure of the main body of the Restorelle DirectFix Anterior mesh is comprised of a lock-knit stitching pattern, which prevents unraveling should the mesh be cut by the surgeon to an alternate shape. The importance of pore size is discussed below in Section 4.4.

4.4 Principles of Operation and Properties of the Device

Synthetic mesh used in the repair of vaginal wall prolapse provides additional mechanical support and increases the durability of surgical results when repairing weakened or damaged tissue. Synthetic mesh may reduce the risk of POP recurrence and reduce the reoperation rate.

Restorelle DirectFix Anterior mesh treats POP by performing two main functions:

1) Creates a mechanical scaffold to stabilize fascial structures in the anterior compartment of the pelvic floor immediately post-surgery; and

[9] FDA: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. FDA Executive Summary. September 8-9, 2011, at 7. (https://wayback.archive-it.org/7993/20170404140406/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf.)

2) Allows native tissue in-growth for long-term support.

It provides a **mechanical scaffold** for anterior POP repair through these key attributes:

1) Restorelle DirectFix Anterior mesh corrects anterior wall descent and resulting protrusion of the bladder into the vaginal canal.

2) It gives support where needed while maintaining elasticity.

3) The mesh strength (tensile, burst, suture pull-out) is sufficient to hold forces of implantation, support the fascial defects, and reinforce when the tissue integration is complete.[10]

4) The mesh knit and pore geometry are stable along the horizontal and vertical axes due to bidirectional isotropy.[11] Thus, the mesh will not distort when properly implanted.

5) If needed, the body of the mesh can be trimmed to the appropriate vaginal length for individual patient anatomy, ensuring proper fit and support.

The Restorelle DirectFix Anterior mesh also allows **tissue in-growth for integration of the mesh with the body's tissue** for long-term performance. Disruption of the tissues during implantation triggers the body's natural healing response which leads to integration of the mesh. Several characteristics of the mesh are critical to allowing tissue integration, such as the material, porosity, density, conformability, and thickness, and each is described below.

1) Material: Restorelle DirectFix Anterior mesh is **100% monofilament polypropylene**, with no color additives.

- As established by results from extensive biomaterials toxicity testing, which includes chemical characterization coupled with a toxicological risk assessment and a full suite of ISO 10993 (International Organization for Standardization) biocompatibility tests, the finished polypropylene device is biocompatible, nontoxic, and has positive toxicological margins of safety against chronic inflammatory responses. The ISO 10993 standards are formally recognized by FDA as consensus standards.[12]

2) Porosity: Restorelle DirectFix Anterior mesh is a **Type 1 macroporous mesh**.

    - It has two types of pores: minor and major interstitial pores, both pore types are greater than 75 microns in size, and as such the Restorelle DirectFix Anterior

[10] Greca FH, Souza-Filho ZA, Giovanini A, et al.. The influence of porosity on the integration histology of two polypropylene meshes for the treatment of abdominal wall defects in dogs. *Hernia* 2008;2:45-9.

[11] Feola A, Pal S, Moalli P, Maiti S, Abramowitch S. Varying degrees of nonlinear mechanical behavior arising from geometric differences of urogynecological meshes. *J Biomech* 2014;47:2584-9.

[12] FDA, Blue Book Memorandum #G95-1, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (May 1, 1995) ; FDA, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff (June 16, 2016) (this guidance supersedes FDA, Blue Book Memorandum #G95-1, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing").

mesh is classified as a Type 1 macroporous mesh based on the Amid classification system.[13]

- The size of mesh pores has been found to directly impact biologic response to mesh.[14,15] Mesh pore size that is greater than 75 µm allows neovascularization, cell migration, and access for macrophages to eliminate bacteria.[16] Biomaterials that contain pore sizes of less than 75 µm may be more prone to being encapsulated,[17] rather than being infiltrated by host tissue, and are more susceptible to infection.[18]

3) Density: Restorelle DirectFix Anterior mesh is an **ultra-lightweight mesh,** based on the Coda classification system,[19] with a density of **19 g/m2** (main body of mesh).

- Ultra-lightweight mesh has been found to elicit an improved host tissue response when compared to heavier weight mesh.[20,21,22,23] The medical device contains a denser knit pattern at the ends of the "arms" of each device to provide a visual and tactile aid in orientating the mesh to the patient's anatomy.

4) Flexibility and Conformity:

- The flexibility and conformability of the mesh reduce interfacial shear stress and may modify subsequent cellular apoptosis and minimize the potential for wrinkling and bunching that can lead to high stress points.[24,25]

5) Thickness: The thickness of Restorelle DirectFix Anterior mesh has been minimized to support tissue in-growth by providing less distance for cells to migrate through the device.

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[13] Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997;1:15-21.

[14] Patel H, Ostergard DR, Sternschuss G. Polypropylene mesh and the host response. *Int Urogynecol J* 2012;23:669-79.

[15] Greca FH, de Paula JB, Biondo-Simões ML, et al. The influence of differing pore sizes on the biocompatibility of two polypropylene meshes in the repair of abdominal defects. *Hernia* 2001;5:59-64.

[16] Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997;1;15-21.

[17] Rosengren A, Bjursten LM. Pore size in implanted polypropylene filters is critical for tissue organization. *J Biomed Mater Res A* 2003;67:918-26.

[18] Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997;1:15-21.

[19] Coda A, Lamberti R, Martorana S. Classification of prosthetics used in hernia repair based on weight and biomaterial. *Hernia* 2012:;6:9-20.

[20] Liang R, Zong W, Palcsey S, Abramowitch S, Moalli PA. Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque. *Am J Obstet Gynecol* 2015;212:174-e1.

[21] Feola A, Abramowitch S, Jallah Z, et al. Deterioration in biomechanical properties of the vagina following implantation of a high-stiffness prolapse mesh. *BJOG* 2013;120:224-32.

[22] Brown BN, Mani D, Nolfi AL, Liang R, Abramowitch SD, Moalli PA. Characterization of the host inflammatory response following implantation of prolapse mesh in rhesus macaque. *Am J Obstet Gynecol* 2015;213(5):668-e1.

[23] Feola A, Abramowitch S, Jallah Z, et al. Deterioration in biomechanical properties of the vagina following implantation of a high-stiffness prolapse mesh. *BJOG* 2013;120:224-32.

[24] Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. *BJOG* 2013;120:233-43.

[25] Barone WR, Amini R, Maiti S, Moalli PA, Abramowitch SD. The impact of boundary conditions on surface curvature of polypropylene mesh in response to uniaxial loading. *J Biomech* 2015;48:1566-74.

4.5 Device Placement

The Restorelle DirectFix Anterior mesh is designed to be attached proximally to the sacrospinous ligament, a well-known fixation point for transvaginal POP repair, and distally to the arcus tendineus of fascia pelvis.

Surgical Steps - Overview:

1) Perform hydro dissection into the sub epithelial layer of the anterior vaginal wall.

2) Perform a full thickness vaginal incision.

3) Trim the mesh to appropriately fit the patient's vaginal dimensions.

4) Ensure the mesh is lying flat and without folding, twisting or curling.

5) Attachments points should include the sacrospinous ligament, arcus tendineus, and vaginal apex at the surgeon's discretion. Mesh should be fixed without excessive tension.

6) Perform cystoscopy to confirm bladder and urethral integrity.

7) Perform a digital rectal exam to confirm rectal integrity and rule out bowel impingement.

4.6 Summary

This description of the Restorelle DirectFix Anterior mesh and its characteristics may be helpful as the Panel considers how surgical mesh design may be a factor that FDA should consider in its assessment of the efficacy, safety, and benefit/risk profile of surgical meshes intended for transvaginal repair of anterior POP. The material, flexibility and conformity, and thickness of a surgical mesh may contribute to surgical mesh performance. In particular, consistent with the statements in FDA's Executive Summary for the 2011 OB-GYN Panel regarding lightweight, macroporous mesh,[26] Coloplast has identified the following key characteristics that have been demonstrated in scientific studies to reduce the inflammatory response and potentially enhance surgical mesh performance:

- Composition of monofilament polypropylene fibers with a macroporous (>75 µm) pore size; and

- Weight, *i.e.*, ultra-lightweight mesh.

[26] FDA: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. FDA Executive Summary. September 8-9, 2011, at 7. (https://wayback.archive-it.org/7993/20170404140406/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf.).

5. UNITED STATES REGULATORY HISTORY – RESTORELLE FOR TRANSVAGINAL TREATMENT OF ANTERIOR POP

Coloplast Corp., a wholly owned subsidiary of Coloplast A/S, distributes Restorelle in the United States. The Restorelle Polypropylene Mesh medical device line was acquired from Mpathy Medical Inc. (Mpathy) on October 29, 2010, and subsequently submitted as a Special Premarket Notification (K103568) that FDA cleared on December 22, 2010. This premarket notification covers the current medical device design for Restorelle DirectFix Anterior mesh.

As discussed in detail below, surgical mesh for transvaginal POP repair, for which Restorelle DirectFix Anterior mesh is indicated, has been extensively analyzed by FDA. Please see **Table 5-1**.

Table 5-1: Regulatory History Regarding Restorelle DirectFix Anterior Mesh

Date	Event
October 20, 2008	FDA issued a Public Health Notification to surgeons regarding reported complications with the placement of transvaginal mesh for POP and stress urinary incontinence (SUI).
October 29, 2010	Coloplast acquired Restorelle Polypropylene Mesh from Mpathy.
December 22, 2010	FDA cleared Coloplast's special premarket notification for Restorelle (K103568).
July 2011	FDA issued an updated safety communication and a white paper titled *Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse*.
September 8-9, 2011	The 2011 Obstetrics and Gynecology Devices Panel of Medical Devices Advisory Committee (OB-GYN Panel) convened to provide input on the risks and benefits of surgical mesh for transvaginal repair of POP and on FDA's proposed regulatory strategies for these devices.
January 3, 2012	FDA ordered manufacturers of surgical mesh for transvaginal repair of POP to conduct prospective postmarket surveillance studies under the authority of Section 522 of the FDCA.
June 13, 2014	The Restorelle 522 Study was posted on ClinicalTrials.gov
January 5, 2016	FDA issued a final order reclassifying surgical mesh for transvaginal POP repair from Class II to Class III.
January 5, 2016	FDA issued a final order requiring manufacturers of surgical mesh for transvaginal POP repair to submit a PMA within 30 months of the order.
July 5, 2018	Due date to file a timely PMA for surgical mesh for transvaginal POP repair.

On October 20, 2008, after a review of medical device reports about all manufacturers' devices, FDA issued a public health notification to surgeons regarding complications with the placement

of transvaginal mesh for POP and SUI. The notification found complications associated with mesh placed transvaginally were rare but could have serious consequences.

In July 2011, FDA issued an updated Safety Communication and a white paper addressing transvaginal POP repair. Collectively, the safety notification and the white paper informed healthcare providers and patients that serious complications associated with surgical mesh for transvaginal repair of POP were not rare. Additionally, the Communication said there was inconclusive evidence that using transvaginally placed mesh in POP repair improved clinical outcomes more than traditional POP repair that does not use mesh.[27,28] Subsequently, FDA convened the OB-GYN Panel in September 2011 to discuss and make recommendations regarding the risks and benefits of transvaginal mesh for POP repair and potential reclassification, and provide input on FDA's proposed regulatory strategies for these devices.[29]

Following the OB-GYN Panel, in January through April 2012 FDA ordered 34 manufacturers of urogynecologic surgical mesh, including Coloplast, to conduct a total of 131 522 studies under the authority of Section 522 of the FDCA.[30] Coloplast submitted its first clinical study plan in June 2012, FDA approved the protocol in May 2013, and subsequent modifications implemented in the clinical study have been reviewed and approved by FDA.

On January 5, 2016, FDA issued two orders related to surgical mesh for transvaginal POP treatment. The first reclassifies surgical mesh for transvaginal POP treatment from a Class II device to a Class III device.[31] The second requires manufacturers of surgical mesh for that indication to file a PMA application by July 5, 2018 and specifies that 12-month outcomes data collected from companies' 522 studies may be used to support the PMAs.[32] The Agency is allowing manufacturers with cleared devices to market their medical devices while FDA reviews the manufacturers' timely submitted PMAs for the surgical mesh devices. The Agency did not remove from the market surgical mesh for transvaginal POP treatment, despite having received comments in response to the proposed order that requested the recall or ban of such devices. At the time, FDA stated that:

> FDA has determined that the safety and effectiveness of surgical mesh for transvaginal POP repair has not been established and that the collection of

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[27] FDA: Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse. July 2011, at 3, 9-10. (https://www.fda.gov/downloads/medicaldevices/safety/alertsandnotices/ucm262760.pdf.)

[28] FDA: Update on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse: FDA Safety Communication. July 13, 2011. (https://www.burgsimpson.com/wp-content/uploads/2018/03/FDA-safety-communication-pelvic-mesh.pdf.)

[29] Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting, 76 Fed. Reg. 41,507, 41,507-08 (July 14, 2011); FDA: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. FDA Executive Summary. September 8-9, 2011, at 1, 25. (https://wayback.archive-it.org/7993/20170404140406/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf); Obstetrics & Gynecology Device Panel: Surgical Mesh Panel Meeting; Surgical Mesh for Repair of Pelvic Organ Prolapse (POP). September 8-9, 2011. (https://wayback.archive-it.org/7993/20170404140420/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM271769.pdf.)

[30] FDA: FDA's Role and Activities. Last updated August 28, 2018. (https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm262301.htm.)

[31] Obstetrical and Gynecological Devices; Reclassification of Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair; Final Rule, 81 Fed. Reg. 353 (Jan. 5, 2016).

[32] Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair, 81 Fed. Reg. 363 (Jan. 5, 2016).

> additional clinical evidence on these devices is needed. Such additional evidence may provide information to allow FDA to impose controls to mitigate the risks and more clearly characterize the benefits of these devices. In addition, **FDA believes there are potential benefits from surgical mesh used for transvaginal POP repair including treatment of POP in appropriately selected women with severe or recurrent prolapse**. As such, FDA has not determined that this device presents 'an unreasonable and substantial risk of illness or injury.'[33] (Emphasis added)

Coloplast filed its PMA application for Restorelle DirectFix Anterior mesh for anterior POP repair by the date required in the order. This PMA application, and those submitted by other manufacturers for anterior POP repair, are currently under review by FDA. Following the January 5, 2016 FDA orders, Restorelle DirectFix Anterior mesh is one of only three surgical mesh medical devices remaining on the market for the transvaginal repair of POP, according to FDA.[34] All three medical devices are intended for repair of anterior POP; there are no surgical meshes remaining on the market for the transvaginal repair of posterior POP.

[33] Obstetrical and Gynecological Devices; Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair; Final Rule, 81 Fed. Reg. 363 (Jan. 5, 2016).

[34] FDA: Urogynecological Surgical Mesh Implants. Last updated December 19, 2018. (https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/urogynsurgicalmesh/.)

6. DESCRIPTION OF THE COLOPLAST SECTION 522 CLINICAL INVESTIGATION (RESTORELLE 522 STUDY)

6.1 Study Identifiers

Coloplast's Restorelle 522 Study is entitled "Restorelle® Transvaginal Mesh versus Native Tissue Repair for Treatment of Pelvic Organ Prolapse 522 Study (Restorelle 522 Study). Study ID SU014." This clinical investigation is sponsored by Coloplast and registered under the identifier NCT02162615 on ClinicalTrials.gov.

6.2 Focus of this Section

The Panel is charged with advising FDA on the factors that the Agency should consider regarding the assessment of the effectiveness, safety, and benefits/risks of surgical mesh medical devices for transvaginal treatment of anterior POP, as well as the appropriate patient population and surgeon training. The Panel is being convened while the FDA is actively conducting its review of a PMA application from Coloplast for the use of surgical mesh intended for transvaginal repair of anterior POP.

Therefore, as the Panel thinks about the factors that FDA should consider, it may be helpful that the Panel consider that FDA, when explaining that 522 studies could serve both a postmarket surveillance purpose and support PMA applications, FDA said in the final PMA order that "the 522 orders requested collection of safety and effectiveness outcomes for surgical mesh for transvaginal POP repair at 6 months, 12 months, 18 months, 24 months, and 36 months following surgery. Therefore, FDA expects that the 522 studies should be designed to collect the 1-year outcomes requested to support premarket approval."[35] Coloplast's postmarket surveillance study, key aspects of which are discussed in this document, will continue to generate data through 36 months post-index procedure.

It may also be helpful for the Panel to appreciate the distinctive features of the design of the Restorelle 522 Study. Among the distinctive features of this real-world postmarket surveillance study are the assignment of subjects to the mesh cohort or the native tissue repair cohort pursuant to pre-enrollment consultation and discussion between the patient and her surgeon to choose the treatment group, rather than randomization, permitted concomitant pelvic surgical procedures, and the absence of blinding.

The 12-month clinical safety and efficacy outcome data of the Restorelle 522 Study are currently under interactive PMA review by FDA. Coloplast also submitted 24- and 36-month follow-up data for those patients that had completed their 24- and/or 36-month follow-up visits at the time of PMA submission; however, such data was not yet available for the majority of patients. Because the purpose of this Panel is not to review either FDA's or a manufacturer's analysis of PMA clinical study outcome data or to determine if a single manufacturer's medical device is safe and effective for the intended use, Coloplast will not present these analyses in this document.

[35] Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair, 81 Fed. Reg. 363 (Jan. 5, 2016).

6.3 FDA Determination: Use of Data from 522 Studies for PMA Submission

In FDA's January 5, 2016 final order requiring PMA applications for transvaginal POP repair (as described in Section 5 of this document), FDA determined that 12-month data collected from the ongoing 522 studies being conducted by Coloplast and other manufacturers would be appropriate to support PMA applications. As stated above, in the final PMA order and in response to a comment questioning the use of 522 studies to serve two purposes (that is, postmarket surveillance and PMA approval), FDA stated that:

> *[T]he 522 orders requested collection of safety and effectiveness outcomes for surgical mesh for transvaginal POP repair at 6 months, 12 months, 18 months, 24 months, and 36 months following surgery. Therefore, FDA expects that the 522 studies should be designed to collect the 1-year outcomes requested to support premarket approval.*[36] (Emphasis added)

In 2018, Coloplast submitted the required PMA application for Restorelle DirectFix Anterior mesh to FDA, which includes the 12-month clinical data collected during this ongoing post-market surveillance study.

6.4 Overall Study Design

The Restorelle 522 Study, and the 522 studies conducted by other manufacturers, were intentionally not randomized or blinded. As the Panel deliberates on the factors that FDA should consider, it is also important that the Panel appreciate key features of this real-world, postmarket clinical study that differ from a more typical randomized, controlled medical device clinical trial.

The Restorelle 522 Study is a prospective, non-randomized, two-cohort, multi-center, post-market clinical study whose objective is to compare the safety and effectiveness of Restorelle DirectFix Anterior mesh to native tissue repair in the treatment of anterior POP. Enrolled subjects are to be followed for 36 months post-index procedure with scheduled follow-up visits at 2, 6, 12, 18, 24, and 36 months post-index procedure.

The study population consists of adult female subjects with POP who are clinically indicated for surgical intervention for pelvic floor reconstruction.

The *primary effectiveness endpoint* is recurrent prolapse at 12 months defined as: (1) recurrent prolapse measured anatomically at the target compartment by leading edge of prolapse beyond the hymenal ring by pelvic organ prolapse quantification (POP-Q) examination performed by an independent examiner; (2) additional surgical treatment for POP in the target vaginal compartment(s); or (3) patient reporting of symptoms of vaginal bulging by the Pelvic Floor Distress Inventory (PFDI-20) questionnaire. If a subject fails any one of the three components, she is considered a surgical failure for the primary effectiveness endpoint.

[36] Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair, 81 Fed. Reg. 363 (Jan. 5, 2016).

The *primary safety endpoint* is the proportion of target compartment device and/or procedure-related serious adverse events (SAEs) at 12 months as determined by the Clinical Events Committee (CEC).

The Restorelle 522 Study is conducted in accordance with United States regulations for the protection of human subjects (21 C.F.R. Parts 50, 54, 56, and 812.280) and in accordance with local regulations and the Declaration of Helsinki concerning research in humans, as applicable to geographies outside the United States.

The study utilizes the Pelvic Floor Disorders Registry (PFDR) sponsored by the American Urogynecologic Society (AUGS) as the data repository. FDA's oversight of the study is managed by the 522 Postmarket Surveillance (PMS) Program within the FDA's DEPI/OSB. This oversight helps ensure well-designed 522 studies are conducted effectively and efficiently. Study sponsors must submit regular (annual) reports that include information on device- or procedure-specific AEs reported during progress of the study, and information, such as population demographics, status of participating clinical sites, and patient enrollment/withdrawal status, among other information.

6.5 Restorelle 522 Study Treatment Assignment

The Restorelle 522 Study, which examines two surgical procedures in common use in the United State for the treatment of POP, is not randomized or blinded. Treatment assignment to surgical repair with either Restorelle DirectFix Anterior mesh or native tissue repair relied on a real-world, pre-enrollment consultation and discussion between the patient and the surgeon to choose the treatment group (as opposed to random assignment). The informed consent form used in the Restorelle 522 Study explains: "Your doctor will clearly explain each procedure and discuss with you what kind of treatment is recommended for your condition. You will decide with your doctor which option is best for you before you agree to participate in the study."

This type of process, sometimes referred to as a shared decision-making process, is actively promoted by the Agency for Healthcare Research and Quality (AHRQ), within the Department of Health and Human Services (HHS), to healthcare providers to consider in the selection of health care options with patients.[37] The following is the procedure used in the Restorelle 522 Study for treatment assignment:

> *This study is not randomized. Patients with POP are counseled on their disease state and informed of treatment options. The patient and physician make the treatment decision based on various factors, including but not limited to, physician expertise, subject preference, need for concurrent procedures, health of the patient's tissue, lifestyle, sexual activity, and various surgical risk factors. Only after the patient and physician agree upon surgical repair with either Restorelle DirectFix Anterior mesh or native tissue repair are patients provided information regarding study participation.*

[37] The SHARE Approach: Essential Steps of Shared Decision-making: Expanded Reference Guide with Sample Conversation Starters. AHRQ. DHHS. April 2014. (https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-2/share-tool2.pdf)

Note: Over the study enrollment period, various regulatory agencies and medical societies issued recommendations and statements concerning the use of transvaginal mesh for POP. In general, these statements recommend active patient participation in the decision-making process, discussion of risks and benefits, and suggest that mesh should be reserved for complex cases, in particular, when other surgical procedures have failed or are expected to fail.

6.6 Concomitant Surgical Procedures

In this real-world postmarket surveillance study, the protocol permits concomitant pelvic surgical procedures, selected based on the clinical needs of the individual patient. Permitted concomitant surgical procedures include, but are not limited to, treatment for POP with native tissue repair in a non-target compartment in a patient assigned to the Mesh arm (*e.g.*, compartment not meeting inclusion criteria), treatment for stress urinary incontinence, and/or concurrent hysterectomy.

6.7 Procedures to Address the Absence of Blinding

In the Restorelle 522 Study, because neither the patient or surgeon are blinded to the choice of the treatment assignment, the study protocol includes specific procedures to mitigate potential bias regarding assessment of the components of the primary effectiveness and safety endpoints.

- Post-procedure, the follow-up Pelvic Organ Prolapse Qualification System (POP-Q) examination for determination of recurrent anatomic prolapse in the target compartment is to be performed by an independent examiner, *i.e.*, a surgeon competent in performing POP-Q measurements who is not the surgical operator.

- An independent CEC, which is external to Coloplast and free of any direct study involvement, is responsible for adjudicating and determining for each site-reported adverse event: (1) whether the event meets the definition of a SAE; (2) whether the event meets the definition of an unanticipated adverse device effect (UADE); (3) the severity of the event; and (4) the relatedness of the event to the index prolapse repair procedure. CEC-adjudicated adverse event data supersedes investigator-reported adverse event analysis in all safety analyses.

7. CHARACTERISTICS OF PATIENTS IN THE RESTORELLE 522 STUDY

7.1 Focus of this Section – Characteristics of Patient Subjects in a Real-World Study

This section focuses on the characteristics of patient subjects in the Restorelle 522 Study, whose design is described in Section 6. As the Panel considers the factors that FDA should consider when evaluating safety, efficacy, and benefit/risk of surgical mesh for transvaginal treatment of anterior POP and the appropriate patient population, the Panel may find it helpful to learn about Coloplast's experience in this study and what it reveals about the contemporary patient population being treated with surgical mesh. This section presents descriptive observations regarding the baseline characteristics of the subjects who enrolled in the Restorelle 522 Study for the transvaginal treatment of anterior POP.

- These observations, based on this post-market surveillance study, may provide the Panel with some helpful insights into how the contemporary practice of medicine affects the choice between the use of mesh or native tissue repair in surgical treatment for anterior POP.

- These observations may also provide some insights into how the pre-enrollment consultation and discussion between patient and surgeon to choose the patient's treatment group in this real-world clinical study impacted the distribution of clinical characteristics of the patients who enrolled in the study.

Because the analyses of the endpoints of the study are under PMA review by FDA and the purpose of this advisory committee meeting is not the review of an individual manufacturer's or the FDA's analyses of PMA endpoint data, preliminary analyses of study endpoints will not be presented at this Panel meeting.

7.2 Observations – Sites and Enrollment

Coloplast submitted data from the Restorelle 522 Study to FDA in the PMA submission for Restorelle for the transvaginal treatment of anterior POP. The study data were collected from 44 study sites, with first subject enrollment on September 17, 2014. In the PMA submission, a total of 426 subjects comprise the modified intent to treat (mITT) population specified by the protocol for the analysis at 12 months. There are 218 subjects in the mesh arm (Mesh arm) and 208 subjects in the native tissue repair arm (NTR arm).

The Restorelle 522 Study was and continues to be conducted at the 44 study sites in the United States, Canada, Netherlands, Australia, Belgium, and France. Thirty sites (68%) are in the United States. The sites represent diverse geographies and types of healthcare systems. The Principal Investigator for the United States and Canada is Dr. James Chivian Lukban, DO, FACOG, FACS, and the Principal Investigator for the European Union and Australia is Prof. dr. Johannes Paulus Roovers.

7.3 Observations – Characteristics of Patients

Baseline patient characteristics including POP-Q stage, bowel symptoms, prior conservative care for POP, and medical history regarding non-gynecologic conditions were largely similar between the Mesh arm and the NTR arm.

Patients in the Mesh arm tended to be older and were more likely to be postmenopausal, no longer engaging in sexual activity, receiving estrogen therapy, and to have vaginal atrophy. Also, patients in the Mesh arm were more likely to have undergone previous pelvic surgery, including hysterectomy. The most notable difference at baseline was that nearly three-fold more patients in the Mesh arm had undergone prior pelvic surgery to treat prolapse compared with patients in the NTR arm; of the patients in Mesh arm, a majority had undergone prior surgery for repair of the anterior and apical compartments.

Coloplast also observed a difference in the patient populations in the two arms regarding the types of concomitant surgical procedures that were performed in addition to anterior POP repair in the study. Of those patients who received a concomitant surgical procedure, more patients in the NTR arm received a concomitant hysterectomy whereas a greater number of patients in the Mesh arm received concomitant surgical treatment for SUI.

7.4 Considerations – Real-World Study Design and Choice of Treatment Arm

These observations underscore the fact that the Restorelle 522 Study is not a typical randomized clinical trial in which patient characteristics and confounding variables, such as the history of prior surgery for POP and concomitant surgical procedures, are equally distributed between the groups.

Rather, the Restorelle 522 Study is a real-world clinical study and the assignment of patients to treatment arms is likely to reflect contemporary practice patterns and choices regarding anterior POP repair when views and preferences of both the patient and the surgeon are used to determine the choice of therapy. Consistent with the real-world design of this study, the study was deliberately not designed to narrowly compare only the use of mesh or native tissue repair for repair of the anterior vaginal compartment. Instead, based on the pre-enrollment consultation between patient and surgeon and the real-world needs of the patient, concomitant surgery in addition to anterior POP repair was permitted by the study protocol, was commonly performed, and the types of concomitant surgery differed between the groups.

Throughout the study enrollment period, various regulatory agencies and medical societies released statements and recommendations to surgeons and patients concerning the use of synthetic mesh for transvaginal POP repair. For example, while enrollment in the study was ongoing, FDA issued extensive information and recommendations to both patients and surgeons regarding the use of surgical mesh for transvaginal repair of POP.[38] Such statements and

[38] FDA, Urogynecologic Surgical Mesh Implants; Information for Health Care Providers for POP: Recommendations for Health Care Providers Treating Pelvic Organ Prolapse, https://wayback.archive-it.org/7993/20170111231234/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345204.htm (last updated January 5, 2017); FDA, Urogynecologic Surgical Mesh Implants; Information for Patients for POP: Recommendations for Women with Pelvic Organ Prolapse, https://wayback.archive-

recommendations may have been part of the surgeons' and patients' considerations during their consultation and discussion to choose the patient's treatment assignment.

The disparity in prior prolapse surgery between the groups may reflect differences in practice patterns driven in part by recommendations from regulatory agencies or medical societies and/or the surgeons' and patients' beliefs that patients with a prior history of prolapse failure may be at a greater risk for failure in a repeat procedure, and, therefore, more suitable candidates for treatment augmented with Restorelle DirectFix Anterior mesh. Similarly, the more frequent selection of native tissue repair in younger, non-menopausal patients without prior pelvic reconstructive surgery may also reflect patient and surgeon preference based on a perception that such a patient may have a greater likelihood of post-procedure healing without the need for structural reinforcement by mesh.

7.5 Key Take-Aways

- In its deliberations, the Panel may wish to consider what factors it will recommend that FDA consider regarding the assessment of clinical data from the manufacturers' 522 studies. In doing so, the Panel should keep in mind that the studies are based on real-world, non-randomized study design and pre-enrollment consultation and discussion between the surgeon and patient to choose the treatment group (as opposed to random assignment).

- The characteristics of subjects in the Mesh arm and NTR arm of the Restorelle 522 Study also suggest that surgical practice regarding anterior POP repair has evolved since 2011, when FDA convened the OB-GYN Panel on the subject of the use of surgical mesh for POP repair. Overall, there appears to be a trend to select the use of surgical mesh for those patients who require surgical repair of anterior POP and who may be at higher risk for poor tissue healing with the potential need for increased support, for example, patients with prior surgery for POP.

it.org/7993/20170111231235/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345205.htm (last updated January 4, 2016).

8. POSTMARKET MEDICAL DEVICE REPORTING REVIEW: COLOPLAST EXPERIENCE WITH TRANSVAGINAL TREATMENT OF ANTERIOR POP

Coloplast believes that postmarket surveillance information reported to FDA as Medical Device Reports (MDRs) is valuable to the Panel in its consideration of the benefit/risk profile of surgical mesh for transvaginal repair of anterior POP. There is no comparable MDR data associated with native tissue repair procedures because native tissue is not a medical device and so there are no requirements to file MDRs for native tissue.

To that end, below, Coloplast provides an analysis of MDRs specific to Coloplast's Restorelle mesh intended for the transvaginal treatment of anterior POP.

Importantly, MDRs *do not* necessarily reflect a conclusion by the manufacturer or by FDA that the device, or the manufacturer or its employees, caused or contributed to the reportable event.[39]

8.1 Overview of MDR Requirements in the United States

Pursuant to Section 519(a) of the FDCA and its implementing regulations, 21 C.F.R. Part 803, manufacturers of medical devices, among other mandatory reporters (*i.e.*, device user facilities and importers), are required to identify and monitor significant events and to submit to FDA reports for certain events and medical device malfunctions involving medical devices.[40] The regulations provide FDA and manufacturers a mechanism to detect and correct problems with a medical device in a timely manner.

A manufacturer of a medical device marketed in the United States must review and evaluate all information received about the performance of its devices to determine if such information constitutes a "complaint." A "complaint" is defined as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution."[41] All complaints must be evaluated to determine if the complaint constitutes an MDR reportable event.[42]

An "MDR reportable event" is an event about which a manufacturer has received or otherwise has become aware of information that reasonably suggests that one of its marketed devices device may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.[43] If a manufacturer markets the device in the United States, a MDR reportable event occurring outside the United States is required to be reported in the same manner.

Within these FDA regulations, FDA provides definitions to ensure proper reporting. FDA defines "***caused or contributed***" to mean a death or serious injury was or may have been

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[39] *See* 21 C.F.R. § 803.16 (2015) (The reporting entity "may deny that the report or information submitted ... constitutes an admission that the device, you, or your employees, caused or contributed to a reportable event.").

[40] *See* 21 U.S.C. § 360i (2019); 21 C.F.R. § 803 (2018).

[41] 21 C.F.R. § 820.3(b) (2013).

[42] 21 C.F.R. § 820.198(a)(3) (2013).

[43] *See* 21 C.F.R. § 803.50(a) (2015).

attributed to a medical device or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of: failure; malfunction; improper or inadequate design; manufacture; labeling; or user error.[44] A "***serious injury***" is defined as an injury or illness that: is life threatening; results in permanent impairment of a body function or permanent damage to body structure; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.[45] Finally, FDA regulations define a "***malfunction***" as the failure of a device to meet its performance specifications or otherwise perform as intended.[46] Performance specifications encompass not only technical operating specifications, but also include all claims made in the labeling for the device. Intended performance refers to intended use for which the device is labeled or marketed.

Manufacturers of medical devices marketed in the United States are required to submit a report to FDA for MDR reportable events within 30 calendar days.[47] A manufacturer, however, is not required to report a death or serious injury if: (1) it is determined that the information received is erroneous; (2) a person qualified to make a medical judgment (*e.g.,* a surgeon, nurse, risk manager, or biomedical engineer) reasonably concludes that the device did not cause or contribute to a death or serious injury or that a malfunction would not be likely to do so if it were to recur; or (3) it is determined that the device was manufactured by another manufacturer.[48]

The mandatory MDRs submitted to FDA by manufacturers, importers, and device user facilities and voluntary reports submitted by healthcare professionals, patients, and consumers are housed in FDA's Manufacturer and User Facility Device Experience (MAUDE) database. This information is publicly available. Importantly, FDA recognizes that "MAUDE data is not intended to be used to either evaluate rates of adverse events or compare adverse event occurrence rates across devices."[49]

As discussed in more detail below, Coloplast searched FDA's MAUDE database for MDRs reported for Restorelle mesh used in the transvaginal treatment of anterior POP. As FDA previously convened its OB-GYN panel in September 2011 to discuss the benefits and risks of transvaginal mesh for POP repair, Coloplast focuses its review below for MDRs from January 2012 through November 2018.

8.2 Overview of Coloplast's Postmarket Surveillance of MDRs for Transvaginal Treatment of Anterior POP

As required by the FDCA and its implementing regulations, Coloplast engages in postmarket surveillance of its marketed devices intended for the transvaginal treatment of anterior POP, including Restorelle DirectFix Anterior mesh. Pursuant to FDA regulations, Coloplast reviews, evaluates, and investigates, when necessary, any complaints it receives, including an evaluation

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[44] 21 C.F.R. § 803.3 (2015).

[45] 21 C.F.R. § 803.3 (2015).

[46] 21 C.F.R. § 803.3 (2015).

[47] 21 C.F.R. § 803.50 (2015); 21 C.F.R. § 803.53 (2015) (An MDR reportable event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health or for which FDA has made a written request must be submitted within 5 working days.).

[48] *See* 21 C.F.R. § 803.20(c)(2) (2015).

[49] *See* FDA: Manufacturer and User Facility Device Experience Database – (MAUDE). Last updated September 11, 2018. (https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/reportingadverseevents/ucm127891.htm)

to determine whether the complaint represents an event which meets requirements for reporting to FDA under 21 C.F.R. Part 803. Any complaint that represents an event which must be reported to FDA is promptly reviewed, evaluated, investigated, and reported. Coloplast also monitors, tracks, and trends complaints on a routine basis to monitor signals for any problems or concerns associated with its marketed devices, regardless of reportability determinations.

Coloplast completed a search of FDA's MAUDE database for MDRs reported from January 2012 through November 2018 for Coloplast's surgical mesh devices intended for the transvaginal treatment of anterior POP, including Restorelle DirectFix Anterior mesh. Coloplast searched the database for product codes FTL and FTM, the FDA classification codes that may be applicable to surgical mesh devices used for transvaginal POP repair.[50] Coloplast reviewed each report that the search returned and identified those reports that were Coloplast specific. The Company then removed any reports that were not specific to treatment of POP in the anterior compartment. Coloplast confirmed that these MDRs identified from FDA's MAUDE database were also included in Coloplast's internal database.

Coloplast recognizes—as FDA recognizes—certain limitations of MAUDE data analysis exist, including:

- Duplicate reports may exist in the data. For example, if one event has two reports (*e.g.*, one report from a manufacturer and a second report from a user), but they are not linked in the MAUDE database as one event, these events will be identified in MAUDE as two separate reports.

- Many voluntary reporters use lay terminology to describe their events, report incorrect procedure(s), and/or identify the incorrect manufacturer or brand names, among other reporting errors, and therefore certain reports might be misclassified or misattributed to a particular device.

However, Coloplast does not believe that either of these limitations and the resulting groups of reports are frequent enough to affect the overall information that can be extracted from search results.

As discussed in more detail below, the search Coloplast conducted identified 211 MDRs that were specific to Restorelle intended for the transvaginal treatment of anterior POP across the nearly seven-year search period.

As discussed in Section 4, Restorelle DirectFix Anterior mesh is a permanent, macroporous, synthetic implant constructed of medical grade, knitted, non-absorbable, monofilament polypropylene. Restorelle DirectFix Anterior mesh is an ultra-lightweight, Type 1 mesh (per the Amid classification system for biomaterials) with monofilament polypropylene fibers that are weaved into a macroporous (>75 µm) architecture. Indeed, these key technical features of Restorelle DirectFix Anterior mesh help to optimize its efficacy and safety for transvaginal anterior POP repair, which Coloplast believes is an important factor in the small number of MDRs related to the use of Restorelle intended for the transvaginal treatment of anterior POP.

[50] Upon reviewing the product codes FTL and FTM, all MDRs specific to Coloplast devices used for the transvaginal treatment of anterior POP were identified under the product code FTL.

8.3 Time-based Trend of MDRs Relating to the Use of Coloplast Devices for the Transvaginal Treatment for Anterior POP using FDA's MAUDE Database

8.3.1 Number of MDRs Per Year

The number of MDRs received by FDA per year from January 2012 through November 2018 specific to Restorelle used for the transvaginal treatment of anterior POP, including those reportable events from ongoing 522 studies, are presented in **Table 8-1**.

Table 8-1: Number of MDRs Associated with Coloplast Surgical Mesh Devices Used in the Treatment of Anterior POP Per Year, January 2012 through November 2018

Year	Number of MDRs*
2012	3
2013	20
2014	33
2015	32
2016	102
2017	16
2018 (January-November)	5
Total	**211**

* The number of MDRs submitted to FDA by Coloplast each year varies due the reports of events received through product liability litigation.

There were no deaths reported in the MAUDE database during the search period for patients implanted with Restorelle used for the transvaginal treatment of anterior POP for which the patient's death was caused or contributed to by the Coloplast device. There were also no malfunctions identified in the MAUDE database search for patients implanted with a Restorelle for the transvaginal treatment of anterior POP in which the malfunction was attributed to the Coloplast device.

Multiple factors can impact MDR reporting, including—as FDA recognizes—the increased use of urogynecologic surgical mesh in clinical community, increased awareness of potential events associated with mesh after FDA's 2008 Public Health notification and 2011 Safety Communication, and an increase in the number of actual events associated with mesh; however, the number of MDRs reported to FDA for Restorelle intended for the transvaginal treatment of anterior POP are consistently low in each year from January 2012 through November 2018.

8.3.2 Events Submitted in Medical Device Reports

The Company reviewed the 211 MDRs associated with Coloplast surgical mesh devices used in the treatment of anterior POP that were identified in the search described above to analyze the events reported. Each MDR may be associated with one or more reported events. The events reported for Restorelle indicated for the transvaginal treatment of anterior POP are presented in

Table 8-2, along with the respective percentage of the total events reported. During the Company's discussion with FDA relating to the Restorelle 522 Study, FDA stated that it was concerned with the following events: bleeding, dyspareunia, dysuria, erosion, exposure, extrusion, fistula formation, infection, pain, prolapse recurrence/repair ineffective, resurgery, retention, scarring, urge incontinence, urinary retention/urethral obstruction or erosion, and vaginal scarring. *Thus, for ease, in Table 8-2 Coloplast highlighted those events that FDA has identified of particular interest.*

Table 8-2: Events Reported in MDRs Associated with Coloplast Surgical Mesh Devices Used in the Treatment of Anterior POP, January 2012 through November 2018

Events	Total Reported	% of Total Events Reported in MDRs
Bleeding	49	4.2%
Continued incontinence	13	1.1%
Delayed procedure	1	0.1%
Discomfort (*e.g.*, bloating)	5	0.4%
Dyspareunia	97	8.3%
Dysuria	19	1.6%
Erosion	90	7.7%
Excessive tissue damage	1	0.1%
Exposure	72	6.1%
Extrusion	24	2.0%
Fistula formation	3	0.3%
Hematoma	14	1.2%
Hematuria	5	0.4%
Infection	116	9.9%
Inflammation	7	0.6%
Irritant to patient	2	0.2%
Local irritation/fever	6	0.5%
Migration	2	0.2%
Pain	178	15.2%
Perforation	4	0.3%
Prolapse recurs/repair ineffective	92	7.8%
Recurrent incontinence	62	5.3%
Resurgery	182	15.5%
Retention	29	2.5%
Scarring	13	1.1%
Urge incontinence	23	2.0%
Urinary retention/urethral obstruction or erosion	3	0.3%
Vaginal extrusion of mesh/suture	6	0.5%
Vaginal scarring	28	2.4%
Worsened incontinence	27	2.3%
Total	**1173**	

Although multiple factors can impact the events reported, including—as FDA recognizes—the increased use of urogynecologic surgical mesh in clinical community, increased awareness of potential events associated with mesh after FDA's 2008 Public Health notification and 2011 Safety Communication, etc., the most frequent events (*i.e.*, those events that represent over 5.0% of the total events reported) reported to FDA after the use of Restorelle intended for the transvaginal treatment of anterior POP include: resurgery; pain; infection; dyspareunia, erosion, prolapse recurs/repair ineffective, exposure, and recurrent incontinence.

8.4 Summary of MDR Trends

Although Coloplast's review of the MDRs submitted to FDA for Restorelle intended for transvaginal anterior POP repair represents a real-world risk profile, Coloplast recognizes the analysis is specific to the use of Coloplast's Restorelle medical devices used for the transvaginal treatment of anterior POP and may not fully reflect the risk profile of other surgical mesh devices that differ from Restorelle in relevant features of the device design. However, specific to Coloplast's experience, MDRs associated with Restorelle intended for transvaginal anterior POP repair reflect a small number of occurrences when compared to the total number of device implantations. And although MDR rates vary slightly year to year, it is Coloplast's experience that the most frequent events have remained consistent over the years. The Company's MDR assessment confirms—for Restorelle intended for the transvaginal treatment of anterior POP—that the events are well-understood and reasonably defined and, after a decade of real-world experience, the likelihood is low that any new events will be identified for Restorelle used for transvaginal anterior POP repair.

Importantly, Coloplast recognizes that certain anticipated events associated with anterior POP surgical treatment, whether augmented with surgical mesh or via native tissue repair, can be serious and have potential for serious long-term effects. However, Coloplast believes that there are factors that can mitigate the probability of an event occurring and improve the benefit-risk profile. These factors include, among other things, labeling of mesh medical devices that includes appropriate warnings, precautions, and indications; informed decision-making between the surgeon and patient; and proper surgical technique.

9. CLINICAL LITERATURE REVIEW AND EVALUATION

9.1 Focus of this Section

As explained earlier in this document, Restorelle DirectFix Anterior mesh, and similar medical devices, have been cleared by FDA for surgical use in the United States for the transvaginal repair of anterior POP for over a decade. A benefit of this long use history is that clinicians have been able to study the outcomes of their patients who underwent surgical procedures augmented with mesh and publish clinical investigations about the observed performance and efficacy of the devices and related procedures. These contemporary clinical studies that address the performance and safety of surgical mesh medical devices used for transvaginal treatment of anterior POP may be useful for the Panel members to consider during their deliberations about the factors that FDA should consider in its assessment of the efficacy, safety, and benefit/risk profile of these medical devices. To that end, Coloplast conducted a comprehensive literature search in PubMed to identify data relevant to Restorelle DirectFix Anterior mesh, and the results are presented here for the Panel's benefit.

Previous literature searches, like the one discussed in FDA's 2011 Executive Summary[51] provided to the OB-GYN Panel in preparation of the September 8-9, 2011 advisory committee meeting, may no longer provide an accurate depiction of the safety and effectiveness of medical devices for the transvaginal repair of anterior POP that are currently marketed. The findings in those earlier literature searches are influenced by studies of medical devices with inferior biomechanical properties to the surgical meshes marketed today and implanted with surgical techniques that are no longer utilized and may be considered obsolete. Coloplast believes that it is critically important for the Panel to only consider the latest generation of devices and current surgical techniques.

Specifically, a variety of characteristics are known to affect the performance of a surgical mesh device for repair of POP including the type of material, density, and porosity of the mesh.[52,53,54,55,56,57] In addition, the surgical approach (*e.g.*, transvaginal, single-incision, use of fixation) may affect clinical outcomes.

Restorelle DirectFix Anterior mesh was purposefully designed for POP repair. As an ultra-lightweight, macroporous, Type 1 mesh, Restorelle possesses all of the characteristics recognized

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51 FDA: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence; FDA Executive Summary. September 8-9, 2011, at 16-23, 58. (https://wayback.archive-it.org/7993/20170404140406/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf)

52 Barone WR, Moalli PA, Abramowitch SD. Textile properties of synthetic prolapse mesh in response to uniaxial loading. *Am J Obstet Gynecol* 2016;215:326.e1-9.

53 Jallah Z, Liang R, Feola A, et al. The impact of prolapse mesh on vaginal smooth muscle structure and function. *BJOG* 2016;123:1076-85.

54 Brown BN, Mani D, Nolfi AL, Liang R, Abramowitch SD, Moalli PA. Characterization of the host inflammatory response following implantation of prolapse mesh in rhesus macaque. *Am J Obstet Gynecol* 2015;213:668.e1-10.

55 Liang R, Zong W, Palcsey S, Abramowitch S, Moalli PA. Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque. *Am J Obstet Gynecol* 2015;212:174.e1-7.

56 Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. *BJOG* 2013;120:233-43.

57 Greca F, Souza-Filho Z, Giovanini A, et al. The influence of porosity on the integration histology of two polypropylene meshes for the treatment of abdominal wall defect in dogs. *Hernia* 2008;12:45-9.

as relevant.[58] Therefore, this literature review includes only publications concerning Restorelle DirectFix Anterior mesh and other surgical mesh devices with similar clinical, technical, and biological characteristics to Restorelle DirectFix Anterior mesh. Similar device characteristics were defined as the following: non-absorbable, monofilament, polypropylene, ultra-lightweight,[59] macroporous,[60] and utilizing the transvaginal surgical approach. *See* the protocol for the literature search in **Appendix-Section 9** at the end of this section. In brief, studies published in full in peer-reviewed journals meeting the following criteria were selected for review:

Inclusion criteria

- Full text article available
- Human subject clinical study
- Treated condition includes anterior POP with/without apical support
- Study evaluates the safety and/or performance of Restorelle DirectFix Anterior mesh or a similar device through a minimum of 12-months follow-up

Exclusion criteria

- Animal study or experimental model
- Surgical technique paper or describes a non-standard surgical procedure
- Unable to confirm the use of Restorelle DirectFix Anterior mesh or a similar device
- General reviews, letters, responses, editorials, viewpoints, commentaries, white papers
- Conference papers, presentations, posters, videos, and abstracts
- Not original research or relies on previously published data (*i.e.*, meta-analyses, systematic reviews)

Filters

- Date range: 01 January 2011 to 30 November 2018
- Language: English

9.2 Search Results

A total of 185 citations were retrieved and evaluated for inclusion in this review. After abstract and/or full-text assessment, 16 peer-reviewed publications met the selection criteria and are considered relevant to single-incision, transvaginal, ultra-lightweight polypropylene mesh. Two studies compare a similar mesh device to native tissue repair and 14 studies provide information about patient outcomes within a relevant mesh cohort without a comparison to NTR. A majority

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[58] *See* FDA: Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. FDA Executive Summary. September 8-9, 2011, at 7. (https://wayback.archive-it.org/7993/20170404140406/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf)

[59] Coda A, Lamberti R, Martorana S. Classification of prosthetics used in hernia repair based on weight and biomaterial. *Hernia* 2012;16:9-20. Density classifications: Ultra-light <35 g/m^2, Light ≥35 <70 g/m^2, Standard ≥70 <140 g/m^2, Heavy ≥140 g/m^2.

[60] Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997;1:15–21.

of the studies (94%), describe the clinical outcomes associated with Elevate Anterior & Apical Prolapse Repair System, a device determined to be similar to Restorelle DirectFix Anterior mesh and which is no longer commercially available.

9.3 Characteristics and Limitations of the Relevant Literature

Full abstracts of the relevant literature are provided below. Anatomical outcomes are presented through the POP-Q classification system and subjective outcomes through a variety of recognized instruments, including measures of quality of life, patient satisfaction, and various symptom assessments. The studies enrolled from 42 to 270 patients followed for a minimum of 12 months (range: 12 to 60 months). Collectively, the relevant studies represent outcomes in over 1800 patients. In this summary, AEs are listed as reported by investigators (**Tables 9-1** and **9-2**); in addition, reported events considered by the authors as potentially mesh-related are presented descriptively by the number of studies reporting the event with the range (**Table 9-3**).

A degree of heterogeneity exists across the reviewed literature. The definition of treatment success varies, but a majority of the authors report both objective and subjective outcome measures. In addition, some studies include patients who received treatment in the posterior compartment in addition to the anterior compartment (*i.e.*, total repair), and, in some cases, the investigators do not attribute outcomes to a specific vaginal compartment. Further, the terms used to identify mesh extrusion vary across studies and were not always consistent with current guidance.[61] These events are listed as reported by the authors (**Tables 9-1** and **9-2**); however, for summarization purposes (**Table 9-3**), event descriptions used by authors are harmonized to the current standard. Moreover, the frequency of concomitant procedures—such as hysterectomy and SUI sling—and the use of mesh as a primary or secondary surgery varies across the reviewed studies, and those differences may contribute to differences in clinical performance and/or safety of surgical mesh.

9.4 Clinical Study Observations

Comparative Clinical Studies

Two studies [references 1, 2] compare the use of a mesh device similar to Restorelle DirectFix Anterior mesh to native tissue repair (Table 9-1). The comparator groups include sacrospinous fixation and anterior colporrhaphy. In both studies, the use of mesh resulted in significant improvement in anatomical success within the anterior compartment as compared to native tissue repair. One of the studies [2] reported comparable results within the apical compartment. Subjective outcome assessments demonstrated improvements from baseline in both groups with Lo et al. (2017) [1] finding improved bulge symptoms within the mesh-arm as reported through the POP distress inventory 6 (POPDI-6). Rates of AEs were low and largely similar between groups.

[61] Haylen BT, Maher CF, Barber MD, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). *Int Urogynecol J* 2016;27:165-94.

Both studies assessed mesh exposure/extrusion rate. The rate of mesh exposure/extrusion was low, with Su et al. (2014) [2] reporting a mesh extrusion rate of 0% and Lo et al. [1] reporting a mesh extrusion rate of 3%, which resulted in one case (1%) of mesh revision.

The full published abstracts for both studies are reprinted below.

9.4.1 Lo et al. (2017) [1]

OBJECTIVE: To compare the clinical efficacy, recurrence, complications and quality of life changes 3 years after Elevate-A/single incision mesh surgery anterior apical (SIM A) and sacrospinous ligament fixation (SSF) in the management of POP.

MATERIALS AND METHODS: A prospective cohort study, 139 women, underwent transvaginal surgery for anterior and/or apical POP > stage 2, 69 patients had SIM A and 70 patients had SSF. The objective cure was defined as POP ≤ stage 1 anterior, apical according to POP-Q. Subjective cure is patient's negative feedback to question 2 and 3 of POP distress inventory 6 (POPDI-6). Patient's satisfaction was reported using validated quality of life questionnaires. Multi-channel urodynamic study was used to report any voiding problems related to the prolapse surgery 6 months after surgery.

RESULTS: 119 patients completed a minimum of 3 years follow-up. 89.8% is the overall prolapse correction success rate for SIM A and 73.3% for SSF group ($p = 0.020$), and 96.6% versus 73.4% at the anterior vaginal compartment respectively ($p \leq 0.001$). Statistically significant difference was noticed in apical compartment with 98.3% with SIM A and 85.0% with SSF ($p = 0.009$). The subjective success rate, 86.4% in the SIM A and 70.0% in the SSF arm ($p = 0.030$) was significantly noted. Only, POP distress inventory-6 (POPDI-6) showed significant improvement. Operation time and intra-operative blood loss tend to be more with SIM A.

CONCLUSION: SIM A has better 3 years objective and subjective cure rate than SSF in the anterior and/or apical compartment prolapse.

9.4.2 Su et al. (2014) [2]

INTRODUCTION AND HYPOTHESIS: To compare the efficacy and safety of the Elevate™ anterior and posterior prolapse repair system and traditional vaginal native tissue repair in the treatment of stage 2 or higher POP.

METHODS: A cohort study was conducted between January 2010 and July 2012. Patients who underwent transvaginal pelvic reconstruction surgery for prolapse were recruited. The primary outcome was anatomical success 1 year after surgery. The secondary outcome included changes in the quality of life and surgical complications. Recurrence of prolapse was defined as stage 2 or higher prolapse based upon the POP quantification system.

RESULTS: Two hundred and one patients (100 in the Elevate™ repair group and 101 in the traditional repair group) were recruited and analyzed. The anatomical success rate of the anterior compartment was significantly higher in the Elevate™ repair group than in the traditional repair group (98 % vs 87 %, $p = 0.006$), but not for the apical (99 % vs. 96 %,

p = 0.317) or posterior (100 % vs 97 %, p = 0.367) compartments after a median 12 months of follow-up. Both groups showed significant improvements in the quality of life after surgery with no statistical difference. Mesh-related complications included extrusion (3 %) and the need for revision of the vaginal wound (1 %). Those in the mesh repair group had a longer hospital stay (p = 0.04), operative time (p < 0.001), and greater estimated blood loss (p = 0.05). Other complications were comparable with no statistical difference.

CONCLUSIONS: The Elevate™ prolapse repair system had a better 1-year anatomical cure rate of the anterior compartment than traditional repair, with slightly increased morbidity.

Table 9-1: Summary of Literature Comparing Ultra-Lightweight Mesh to Native Tissue Repair

First Author, Year / Sample Size (n)	Design/ Patient f/u	Mesh Device	Comparator	Outcome Measures		Adverse Events
				Anatomic	Subjective	
Lo 2017 [1] N=139 (Elevate mesh group=69)	Prospective cohort 36-months	Elevate A	Sacrospinous ligament fixation (SSF)	POP-Q Success defined as POP ≤ stage 1 Overall success rate Mesh=89.8% SSF=73.3% p = 0.020 Anterior Mesh 96.6% SSF 73.4% p ≤ 0.001 Apical Mesh 98.3% SSF 85.0% p = 0.009	POPDI-6 (negative responses to q2 and q3) Mesh: 86.4% SSF: 70.0% p=0.030	Blood transfusion: Mesh=0%, SSF=0% Major organ injury: Mesh=0%, SSF=0% Operative site infection: Mesh=0%, SSF=1.8% Secondary SUI surgery: Mesh=10.8%, SSF=1.8% Secondary POP Surgery: Mesh=0%, SSF=4.7% Bladder outlet obstruction: Mesh=0%, SSF=0% Mesh exposure: Mesh=0%, SSF NA Recurrence: Mesh=0%, SSF=4.7%
Su 2014 [2] N=201 (Elevate mesh group=100)	Prospective cohort 12-months	Elevate A	Anterior colporrhaphy	Absence POP-Q Stage 2 or higher 12-months post-surgery. Anterior Mesh=98% NTR=87% p = 0.006 Apical Mesh=99% NTR=96% p = 0.317 Posterior Mesh = 100% NTR = 97 %, p = 0.367	QoL defined through UDI, IIQ-7, PISQ-12 Significant improvements from baseline in QoL with no differences between groups	Blood Transfusion: Mesh=0%, NTR=0% Bladder perforation: Mesh=3%, NTR=3% Hematoma: Mesh=1%, NTR=0% Wound infection: Mesh=0%, NTR=1% Wound dehiscence: Mesh=0%, NTR=1% UTI: Mesh=3%, NTR=3% Mesh extrusion=3% (surgical revision of vaginal wound = 1%)

Non-Comparative Clinical Cohort Studies

A total of 14 publications describe outcomes associated with a surgical mesh device similar to Restorelle DirectFix Anterior mesh without comparison to native tissue repair (**Table 9-2**). These studies include single-arm cohorts and comparisons to non-similar mesh devices (*i.e.*, heavier weight) and/or non-similar procedures (*i.e.*, transobturator mesh, transabdominal sacrocolpopexy). In these cases, only studies associated with mesh devices of similar characteristics are included in the analysis in this section. A majority of the studies are retrospective (71%). Eight studies (57%) report data beyond 12 months (range: 12 to 60 months). The reviewed studies report high rates of objective and subjective cure with the longer-term studies finding durable treatment over time. The most common reported event rate is mesh exposure/extrusion with all sites reporting low rates (range: 0 to 7.5%).

The full, published abstracts of all 14 publications are reprinted below.

9.4.3 Duraes et al. (2018) [3]

OBJECTIVE: The aim of the study was to assess 5 years outcome of transvaginal single incision mesh surgery (SIMS) for anterior POP.

STUDY DESIGN: This was a prospective study including all patients from January 2009 to December 2012 who underwent SIMS for symptomatic anterior prolapse stage ≥2, according to POP-Q. Symptoms and quality of life were assessed using validated questionnaires: Pelvic Floor Distress Inventory (PFDI-20), Pelvic Floor Impact questionnaire (PFIQ-7), and Prolapse/ Incontinence Sexual Questionnaire (PISQ-12). Main outcome was subjective success (question 3 of PFDI-20 score = 0). Mesh-related complications, objective and functional outcomes were used as the secondary outcomes.

RESULTS: 270 patients were included in the study. Median follow-up was 5,7 years [4,5-8,2]. Subjective success rate was 86,6% at 5 years. Objective success rate was 53,1% at 5 years. At 5 years, composite failure (subjective + objective) occurred for 17 patients (12%), 7 patients with direct recurrence and 10 with indirect recurrence. Re-treatment was performed in six patients (2,8%; 3 hysterectomies for apical recurrence and 3 posterior repairs for posterior recurrence). One case (0,4%) of asymptomatic mesh exposure occurred. The reoperation rate for mesh-related complications was 3,4%. At 5 years, de novo dyspareunia rate was 11,7%, 3,9% considered as mesh-related. A significant improvement was noted for symptoms and quality of life.

CONCLUSION: Five-year results demonstrate that vaginal mesh surgery provides a durable and safe repair of anterior compartment prolapse with a low rate of mesh-related complications and reoperations. Between the 2- and 5-year follow-up, patient satisfaction and associated improvements in prolapse-specific symptoms were sustained and minimal new morbidity occurred.

9.4.4 Buca et al. (2018) [4]

Female POP is a common condition and the correction of prolapse remains a major challenge for the surgical community. A retrospective study of women with POP

undergoing pelvic reconstructive surgery with the Elevate System followed-up for 48 months. A total of 138 women with POP were included in the study. We observed an objective cure rate of 94.9% for the anterior wall after 4 years' follow-up. The subjective cure rate was 97.1%. Improvement in the urinary symptoms was seen after the surgery: the number of asymptomatic patients increased from 14.5 to 77% after the 4 years of follow-up. We reported no cases of bleeding, hematoma, mesh infection and bowel injury, while we had four cases of bladder injury and one case of sepsis. The mesh extrusion rate was 7.3%, all cases interested the anterior compartment. Postoperative dyspareunia and pelvic pain were rare. In this cohort, the Elevate Prolapse Repair System was associated with excellent long-term results, for both anatomical corrections of prolapse, with a high objective and subjective cure rate and a functional urinary outcome.

9.4.5 Lamblin et al. (2016) [5]

INTRODUCTION AND HYPOTHESIS: To compare apical correction in stage ≥3 cystocele between two mesh kits.

METHODS: This was a retrospective, nonrandomized study that compared two groups matched on anterior/apical POP-Q stage: 84 received Elevate Ant™ single-incision mesh (Elevate Ant group) and 42 Perigee™ transvaginal mesh (Perigee group). Follow-up at 1 and 2 years comprised objective (POP-Q) and subjective (PFDI-20, PFIQ-7, PISQ-12) assessments. The primary endpoint was objective success: 2-year apical POP-Q stage ≤1. Secondary endpoints were anterior POP-Q stage, subjective results and complications.

RESULTS: Groups were comparable in terms of age (66.6 and 64.7 years, respectively; $p = 0.19$), BMI (both 25.4 kg/m2; $p = 0.93$), and history of hysterectomy (7.2 % and 14.3 %; $p = 0.21$) or prolapse surgery (12 % and 14.3 %; $p = 0.72$). Operative time was shorter in the Elevate Ant group (54.1 vs. 62.5 min; $p = 0.048$), and the 2-year objective apical success rate was higher (92.9 % vs. 66.7 %; $p < 0.0001$), with better point C correction (-5 vs. -3.8; $p = 0.006$). Function improved in both groups, with significantly better PFIQ-7 ($p = 0.03$) and PFDI-20 ($p = 0.02$) scores in the Elevate Ant group at 2 years. Vaginal exposure was not seen in the Elevate Ant group but occurred in two patients in the Perigee group ($p = 0.33$). Factors associated with success were age >65 years (OR 7.16, 95 % CI 1.83 - 27.97) and treatment with Elevate Ant mesh (OR 10.16, 95 % CI 2.78 - 37.14). Postoperative stress urinary incontinence rate was greater with the Elevate Ant group (29.8 % and 16.7 %; $p = 0.11$).

CONCLUSIONS: The use of the Elevate Ant mesh was associated with significantly better apical correction at 2 years. Function improved in both groups, but with a significantly better PFDI-20 score in the Elevate Ant group at 1 and 2 years. The postoperative stress urinary incontinence rate, however, tended to be greater in the Elevate Ant group. The results need confirming with longer follow-up of these cohorts and in randomized studies.

9.4.6 Altman et al. (2016) [6]

INTRODUCTION AND HYPOTHESIS: The objective was to assess safety and clinical outcomes in women operated on using the Uphold™ Lite Vaginal Support System.

METHODS: We carried out a 1-year, multicenter, prospective, single cohort study of 207 women with symptomatic POP-Q stage ≥2 apical POP with or without concomitant anterior vaginal wall prolapse. Safety data were collected using a standardized questionnaire. Anatomical outcome was assessed by the POP-Q and subjective outcomes by the Pelvic Floor Distress Inventory after 2 months and 1 year using a one-way repeated measures analysis of variance. Pain was evaluated using a visual analog scale.

RESULTS: The overall rate of serious complications was 4.3 % (9 out of 207 patients), including 3 patients with bladder perforations, 1 with bleeding >1,000 ml, 2 who had undergone re-operations with complete mesh removal because of pain, and 3 surgical interventions during follow-up because of mesh exposure. POP-Q stage ≤1 after 1 year was 94 % and subjective symptom relief was reported by 91 % of patients ($p < 0.001$). Pain after 2 months and 1 year was 60 % lower compared with the preoperative mean ($p < 0.001$). Minor complications occurred in 20 women (9.7 %) and were dominated by lower urinary tract dysfunction. No predisposing risk factors for complications were found.

CONCLUSIONS: The Uphold™ Lite procedure in women with apical POP provided satisfactory restoration of vaginal topography and symptom relief. However, serious complication rates were largely comparable with those of other transvaginal mesh kits.

9.4.7 Marscke et al. (2016) [7]

AIMS: Single-incision transvaginal mesh for reconstruction of Level I and II prolapses in women with recurrent or advanced prolapse. We evaluated functional, anatomical, sonomorphological and quality-of-life outcome.

METHODS: Data were collected retrospectively for preoperative parameters and at follow-up visits. Anatomical cure was assessed with vaginal examination using the ICS-POP-Q system; introital ultrasound scan for postvoidal residual and description of mesh characteristics was performed. We applied a visual analogue scale (VAS) and the German Pelvic Floor Questionnaire to assess quality-of-life.

RESULTS: Seventy women with cystocele (III: 61.3%/IV: 16%), all post-hysterectomy and in majority (81.4%) after previous cystocele repair, were operated using a single-incision transvaginal technique. Overall anatomical success rate was 95.7% with significant improvement in quality-of-life ($p < 0.0001$). Mesh erosion occurred in 5.7%, one patient presented symptomatic vaginal vault prolapse. Postvoidal residual declined significantly (58 vs. 2.9%). Sonographic mesh length was 55.7% of implanted mesh with a wide range of mesh position, but no signs of mesh dislocation. There was no de novo dyspareunia reported, one case of preoperative existing dyspareunia worsened. No severe adverse event was observed.

CONCLUSIONS: We hereby present a trial of a high-risk group of patients requiring reconstruction of anterior and apical vaginal wall in mostly recurrent prolapse situation. Our data support the hypothesis of improved anatomical and functional results and less mesh shrinkage caused by the single-incision technique with fixation in sacrospinous ligament in combination with modification in mesh quality compared to former multi-incision techniques.

9.4.8 Stanford et al. (2013) [8]

Objective: This study aimed to assess the safety and efficacy of the Elevate Anterior/Apical transvaginal mesh procedure in POP repair at 12-months follow-up.

Methods: This prospective, multicenter, multinational study enrolled 142 patients experiencing anterior vaginal prolapse with or without apical descent (POP-Q Q stage II). Each patient received a single-incision transvaginal polypropylene mesh implantation anchored to the sacrospinous ligaments bilaterally. Primary outcome was treatment success defined as POP-Q less than or equal to stage I at 1 year using the Last Failure Carried Forward method. Secondary outcomes included validated quality-of-life measures. Fourteen subjects who received a concomitant posterior apical support procedure were excluded from the analysis.

Results: Of the 128 subjects, 112 (87.5%) completed the 12-months follow-up. The mean age was 64.7 years. The anatomic success rate was 87.7% (95% confidence interval, 80.3%-93.1%) for the anterior compartment and 95.9% (95% confidence interval, 88.5%-99.1%) for the apical compartment. POP-Q measurements (Aa, Ba, and C) improved significantly ($P < 0.001$) with no significant changes to TVL ($P = 0.331$). Related adverse events reported at greater than 2% were mesh exposure (8; 6.3%), urinary tract infection (7; 5.5%), transient buttock pain (5; 3.9%), de novo stress incontinence (5; 3.9%), retention (5; 3.9%), dyspareunia (3; 3.2%), and hematoma (3; 2.3%). All quality-of-life scores significantly improved from baseline ($P < 0.001$).

Conclusions: Twelve-month data show that Elevate Anterior/Apical support procedure completed through a single vaginal incision yields favorable objective and subjective outcomes.

9.4.9 Barros-Pereira et al. (2017) [9]

OBJECTIVE: To compare the effectiveness of anterior POP repair using Prolift (Ethicon, Somerville, NJ, USA) or Elevate (American Medical Systems, Minnetonka, MN, USA) vaginal mesh at 12 months of follow-up.

METHODS: A retrospective study was undertaken using the records for the first 50 Prolift procedures in 2007-2009 and the first 50 Elevate procedures in 2013-2015 performed at a tertiary urogynecology unit in Lisbon, Portugal. Postoperative follow-up occurred at 3, 6, and 12 months. The primary outcome was surgical efficacy using subjective and objective measures (vaginal bulge symptoms and POP quantification system according to the Weber criteria, respectively) at 12 months.

RESULTS: Improvement according to the Weber criteria was noted for 10 (25%) of 40 women in the Prolift group and 21 (48%) of 44 in the Elevate group at 12 months (P=0.032). Additionally, the Ba point was higher with Elevate than with Prolift (-2.2 ± 1.1 vs -1.5 ± 1.5; P=0.031). Vaginal bulge symptoms were reported at 12 months by 7 (18%) women in the Prolift group and 3 (7%) in the Elevate group (P=0.021).

CONCLUSION: Differences in anatomic results were apparent between the two vaginal mesh groups 12 months after surgery.

9.4.10 To et al. (2015) [10]

INTRODUCTION AND HYPOTHESIS: To determine if laparoscopic sacral colpopexy (LSC) offers better apical support with a lower exposure rate than transvaginal mesh surgery with Elevate™.

METHODS: This was a retrospective cohort study comparing patients with apical prolapse (POP-Q point C ≥ -1) who underwent Elevate™ mesh repair (n = 146) with patients who underwent laparoscopic sacral colpopexy (n = 267).

RESULTS: The sacral colpopexy group had a mean age of 59 years and a BMI of 25.7. Patients in the Elevate™ group were older, with a mean age of 63 and a BMI of 26.3. Most of the patients of both groups presented with POP stage III (LSC 73.8% and Elevate™ 87.0%) and their mean POP-Q point C were not significantly different (LSC 1.4 vs Elevate™ 1.2 cm). Operative time was longer in the LSC group (113 vs 91 min, $p < 0.001$), but estimated blood loss was lower (75 cm3 vs 137 cm3, $p < 0.001$). No difference in mesh exposure rate could be found between the two groups at one year (Elevate™ 0.7% vs LSC 2.6%, OR 0.26, 95% CI 0.03 to 2.10, $p = 0.21$). One-year objective cure rate, defined as no descent beyond the hymen, was 97.0% in the LSC group and 96.6% in the Elevate™ group ($p = .81$). The overall recurrence (objective, subjective recurrence or reoperation) was also not different between the groups (LSC 4.5% vs Elevate 4.8%, $p = 0.89$).

CONCLUSION: Transvaginal Elevate™ mesh delivers comparable apical support with a low exposure rate similar to that of laparoscopic sacral colpopexy.

9.4.11 Hsieh et al. (2017) [11]

AIMS: Single-incision vaginal mesh (SIVM) procedures for POP differed in mesh fabrication and implantation that may affect treatment outcomes. We aim to evaluate and compare the safety and effectiveness of two SIVM procedures, and explore factors that may have associations with surgical effectiveness.

METHODS: Our data of using two SIVM procedures for a total (anterior and posterior) vaginal mesh repair were studied. Patients who had ≧stage 2 POP and underwent either Elevate (n = 85) using anchored, lightweight meshes or Prosima procedures (n = 95) using non-anchored, original meshes were assessed. A detailed comparison of 1 year outcomes was made.

RESULTS: Of the 180 patients, 172 (95.6%) attended the 1-year follow-up. Demographic data were similar between groups except a higher average age (64.5 vs 60.4, P = 0.001) was noted in the Elevate (n = 84) group compared to the Prosima (n = 88) group. Surgical results were also similar except a significantly higher objective cure (POP stage ≦1) rate (89.3% vs 78.4%, P = 0.042) was noted in the Elevate group. The safety profile favored Elevate with a lower, but not statistically significant, rate (4.7% vs 12.5%, P = 0.106) of vaginal mesh exposure. After a statistical analysis, we found anatomic recurrence (POP stage ≧2) after the SIVM procedures had strong (P < 0.05) associations with "early surgical cases," "Prosima procedure," "advanced cystocele (Ba > +3 cm)," and "prior prolapse repair," respectively.

CONCLUSIONS: Beyond a learning curve, Elevate performed better than Prosima in POP repair regarding surgical effectiveness. Meanwhile, several predisposing factors that may affect recurrence after SIVM procedures were found.

9.4.12 Yang et al. (2017) [12]

OBJECTIVE: The aim of this study is to compare perioperative parameters and midterm clinical outcomes using two different mesh kits: transobturator vaginal mesh (TVM) (both Perigee and Apogee), versus single incision vaginal mesh (SIM) (combined Elevate anterior/apical system and Elevate posterior/apical system) in treating severe POP.

MATERIALS AND METHODS: This is a retrospective cohort study. During 2008 and 2013, those women with severe POP [POP-Q, Stage III and Stage IV], who received either TVM or SIM operation, were enrolled for cohort comparison. There were 111 patients in the TVM group, and 136 in the SIM group. Those with an incomplete POP-Q record, or who did not complete postoperative urodynamic study were excluded. Perioperative characteristics and outcomes, postoperative urinary symptoms, urodynamic parameters, prolapse recurrence (defined as the leading edge > 0 using the POP-Q system), and mesh extrusion rate were compared.

RESULTS: There were no differences in the operation time, blood loss, hospital stay, and the postoperative visual analog scale for pain. Urodynamic studies showed improvement in bladder outlet obstruction in both groups. The postoperative stress urinary incontinence was significantly higher in the SIM group. The recurrence of prolapse was comparable between the two groups at a median follow-up of 2 years. The mesh extrusion rate was significantly lower in the SIM group.

CONCLUSION: At an average of 2 years of follow-up, the mesh extrusion rate was lower in the SIM group than in the TVM group, but there was no difference in postoperative visual analog scale for pain. The postoperative stress urinary incontinence was higher in the SIM group.

9.4.13 Rogowski et al. (2015) [13]

INTRODUCTION AND HYPOTHESIS: There are few direct comparisons between the first-generation trocar-guided and the second-generation single-incision mesh systems in

the treatment of anterior POP. Hence, the purpose of this retrospective review was to compare 18-month operative success in female patients who had undergone POP surgery with the anterior Prolift (n = 52) or the anterior Elevate mesh (n = 62).

METHODS: Subjective (bulge symptoms) and objective measures (absence of anterior or apical descent beyond the hymen, POP-Q anterior stage 0 or I, no retreatment for POP) were used as the measures of surgical efficacy. Postoperative pelvic floor pain, dyspareunia, de novo overactive bladder (OAB), de novo stress urinary incontinence (SUI), and mesh exposure were addressed as complications of POP surgery.

RESULTS: The two groups did not differ with regard to the subjective and objective measures of the operative efficacy. There were no between-group differences in the proportion of women reporting postoperative pelvic floor pain, dyspareunia, de novo SUI, and de novo OAB symptoms (all p values >0.05). The proportion of patients with postoperative vaginal exposure was significantly higher in the Prolift group (7.7 %) than in the Elevate group (0.0 %; p = 0.02).

CONCLUSIONS: In conclusion, our results suggest that the use of the Elevate system in patients with anterior compartment prolapse results in fewer mesh erosions, but similar efficacy, compared with the Prolift mesh.

9.4.14 Huang et al. (2015) [14]

INTRODUCTION AND HYPOTHESIS: The aim of this study was to assess the 2-year clinical outcomes of pelvic reconstructive surgery with the single-incision Elevate system (American Medical Systems, Minnetonka, MN, USA).

METHODS: This retrospective study was conducted from November 2010 to August 2013, and included 210 patients with POP stage 3 or 4 who underwent pelvic reconstructive surgery with an Elevate system and were followed for 1 to 3 years postoperatively. Assessments included pre- and postoperative POP-Q stage, Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7) and multi-channel urodynamic examinations. Anatomical success was defined as postoperative POP-Q stage 0 or I.

RESULTS: The anatomical success rates were 95 % for the anterior vaginal wall, 99% for the posterior vaginal wall and 94 % for the apical vaginal wall after a median 27 months of follow-up. POP-Q, UDI-6 and IIQ-7 scores, maximal flow rate and post-voiding residual urine all improved significantly after surgery. Complications included 1 case of internal bleeding, 4 cases of mesh exposure, 5 cases of recurrent prolapse that required salvage operations, and 3 cases of urine retention that required intermittent catheterization. There were no bladder or bowel injuries during surgery.

CONCLUSIONS: Pelvic reconstructive surgery with the Elevate system yielded good anatomical outcomes and symptom improvement after 2 years of follow-up.

9.4.15 Long et al. (2015) [15]

OBJECTIVE: This study aims to compare clinical outcomes using the Perigee versus Elevate anterior devices for the treatment of POP.

STUDY DESIGN: One hundred and forty-one women with POP stages II to IV were scheduled for either Perigee (n = 91) or Elevate anterior device (n = 50). Preoperative and postoperative assessments included pelvic examination, urodynamic study, and a personal interview about quality of life and urinary symptoms.

RESULTS: Despite postoperative point C of Elevate group being significantly deeper than the Perigee group (median: -7.5 versus -6; $P < 0.01$), the 1-year success rates for two groups were comparable ($P > 0.05$). Apart from urgency incontinence, women with advanced POP experienced significant resolution of irritating and obstructive symptoms after both procedures ($P < 0.05$), generating the improvement in postoperative scores of Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) ($P < 0.01$). On urodynamics, only the residual urine decreased significantly following these two procedures ($P < 0.05$). Women undergoing Perigee mesh experienced significantly higher visual analogue scale (VAS) scores and vaginal extrusion rates compared with the Elevate anterior procedure ($P < 0.05$).

CONCLUSIONS: With comparable success rates, the Elevate procedure has advantages over the Perigee surgery with lower extrusion rate and postoperative day 1 VAS scores.

9.4.16 Rapp et al. (2014) [16]

PURPOSE: The Elevate® Anterior and Apical Prolapse Repair System is a polypropylene mesh that is anchored through sacrospinous ligament and obturator fascia fixation points. We present a comprehensive evaluation of this prolapse repair system through 2 years with a focus on safety, operative characteristics, and anatomical, subjective and quality of life outcomes.

MATERIALS AND METHODS: A total of 42 women underwent repair of stage II or greater anterior/apical compartment prolapse using the repair system, of whom 2 were lost to followup. Anatomical outcomes were assessed using POP-Q staging. Subjective and quality of life outcomes were assessed by the validated ICIQ (International Consultation on Incontinence Questionnaire)-VS (Vaginal Symptoms), ICIQ-FLUTS (Female Lower Urinary Tract Symptoms) and IIQ-7 (Incontinence Impact Questionnaire-7). Additional outcomes included a 3-day bladder diary and cough test with outcomes assessed preoperatively, at 6 weeks, and at 1 and 2 years.

RESULTS: Mean ± SD blood loss was 93 ± 55 cc and mean operative time was 58 ± 27 minutes. POP-Q points Aa, Ba and C improved from 0.9, 0.8 and -1.3 preoperatively to -2.1, -2.7 and -6.1 cm at 2 years, respectively (each $p < 0.05$). Four patients experienced anatomical recurrence, which was associated in 2 with symptomatic recurrence on the ICIQ-VS. Statistically significant improvements in the ICIQ-VS, ICIQ-FLUTS and IIQ-7 were seen throughout followup. Adverse events included leg pain, vaginal exposure and urinary retention in 1, 2 and 5 patients, respectively.

CONCLUSIONS: The Elevate Anterior and Apical Prolapse Repair System was associated with good anatomical restoration and significant improvements in validated symptom and quality of life indexes through 2 years of assessments. Our experience suggests that the system is a safe, effective surgical procedure in appropriately selected patients. Long-term follow-up is important, given the FDA warning regarding the use of surgical mesh in the repair of POP.

Table 9-2. Summary of Surgical Mesh Literature without Comparison to Native Tissue Repair

First Author, Year /Sample Size (n)	Design/ Patient f/u	Mesh Device	Outcome Measures		Adverse Events/Recurrence
			Anatomic	Subjective	
Duraes 2018 [3] N=270	Prospective 60-months	Elevate A	Success: POP-Q stage <2 (all compartments including non-anterior) All compartments Mesh= 53.1% Anterior-alone Mesh=66%	Primary Endpoint: Absence of bulge per q3 of PFDI-20 Mesh=86.6%	Mesh exposure=0.4% Mesh-related reoperations=3.4% Apical Retreatment=1.4% de novo dyspareunia (mesh-related)=3.9%
Buca 2018 [4] N=138	Retrospective 48-months	Elevate A	Success: POP-Q <2 Mesh=94.9%	Success: Absence of symptomatic recurrent prolapse Mesh=97.1%	Bleeding=0% Abscess=0% Bowel injury=0% Hematoma=0% Bladder injury=2.9% Sepsis=0.7% Mesh extrusion=7.25% (surgical revision=2.2%) Anterior recurrence=0.3
Lamblin 2016 [5] N=126 (Elevate=84)	Retrospective comparison between mesh kits (only Elevate presented) 24-months	Elevate A	Success: POP-Q ≤1 Anterior: Mesh=73.8% Apical: Mesh=92.9%	PFDI-20, PFIQ-7, and PISQ-12 Significantly improved from baseline through 24-months	Mesh exposure=0% Mesh revision=1.2% Postoperative SUI=29.8% Spontaneous vaginal pain=0% Vaginal pain on examination=5.9%
Altman 2016 [6] N=207	Prospective 12-months	Uphold Lite	Success: POP-Q ≤1 Mesh=94%	POPSI, CRAD, UDI All subscales improved Mesh=91%	Bladder perforation=1.5% Urethra or rectum perforation=0% Bleeding ≥500 ml=3.3% Bleeding ≥1000 ml=0.5% UTI=0.5% Bladder-emptying difficulties=5.7% Catheter after discharge=2.4% Anemia=0% Fever ≥3 days=0.5% Wound infection=0% Groin pain=1% Vaginal hematoma=1.4% Deep venous thrombosis=0% Cardiovascular problems=0.5% Pelvic hematoma=1% Re-operation (mesh removal due to pain)=1% Mesh exposure=1.4% Others=1.5%
Marschke 2015 [7] N=70	Retrospective 13-months	Elevate A	Success: POP-Q stage 0 or 1	QoL (German Pelvic Floor Questionnaire),	Blood loss requiring transfusion=0% Mesh erosion=5.7% (1.4% with surgical intervention)

First Author, Year /Sample Size (n)	Design/ Patient f/u	Mesh Device	Outcome Measures		Adverse Events/Recurrence
			Anatomic	Subjective	
			Mesh=95.7%	symptoms, satisfaction (Visual Analog Scale) Subjective parameters improved significantly in all comparisons	de novo SUI=4% de novo Urgency=5.7% de novo dyspareunia = 0% worsened pre-existing dyspareunia=1.4% Pain or discomfort upon palpation=27.1% (none requiring intervention) Recurrence (asymptomatic)=2.9% Mesh dislocation on sonogram=0% Serious adverse events=0%
Stanford 2013 [8] N=142 (Elevate =128)	Prospective 12-months	Elevate A	Success: POP-Q ≤1 Anterior: Mesh=87.7% Apical: Mesh=95.9%	PISQ-12, PFDI, PFIQ-7 All QoL scores improved significantly from baseline	Mesh exposure/extrusion=6.3% UTI=5.5% Transient buttock pain=3.9% de novo SUI=3.9% Urinary retention=3.9% Dyspareunia=3.2% Hematoma=2.3% Granuloma formation=1.6% Pain/discomfort-vaginal=1.6% Urinary retention (transient)=1.6% Constipation=0.8% Dyspareunia (partner)=0.8% Infection=0.8% Pain/discomfort (pelvic)=0.8% Pain/discomfort (urethral)=0.8% Pain/discomfort (urogenital)=0.8% Prolapse recurrence, enterocele=0.8% Ureteral obstruction=0.8% Urinary frequency=0.8% Urinary incontinence – de novo urge=0.8% Urinary incontinence – persistent=0.8% Urinary incontinence – worsening mixed=0.8% Urinary incontinence – worsening stress=0.8% Urinary incontinence – worsening urge=0.8% Urinary urgency=0.8% Wound dehiscence=0.8%
Barros-Pereira 2017[9] N=100 (Elevate=50)	Retrospective 12-months	Elevate A	POP-Q Cured or improved=87%	Vaginal Bulge Symptoms Mesh=7% reporting symptoms	Pelvic floor pain=5% de novo SUI=2% de novo OAB=16% Dyspareunia=5% Constipation=14% Mesh exposure=0%
To 2017 [10] N=267 (Elevate=146)	Retrospective 12-months	Elevate A	Primary: Absence of descent beyond the hymen Mesh=96.6%	Subjective recurrence (included in Recurrence rate reported in column to the right)	Bladder injury=2.1% de novo SUI=11.6% de novo Urgency=6.2% Vaginal/buttock pain=3.4% Mesh exposure=0.7% (excision required) Re-operation for prolapse=4.1% Recurrence=4.8%
Hsieh 2017 [11] N=180 (Elevate=85)	Retrospective 12-months	Elevate A	Success: POP-Q ≤1 Mesh=89.3%	Success: Free of bulge or pressure symptoms and absence of the descent beyond hymen Mesh=92.8%	Pelvic hematoma=2% Prolonged Foley (<7 days) =4.8% de novo/persistent SUI=10.7% de novo/persistent UUI=9.5% Vaginal mesh extrusion=4.8%
Yang 2017 [12] N=247	Retrospective 24-months	Elevate A	Recurrence: Leading edge >0	N/A	Transient post-op ICP=25.7% Post-op SUI=3Ftab% Post-op OAB=35.2%

First Author, Year /Sample Size (n)	Design/ Patient f/u	Mesh Device	Outcome Measures		Adverse Events/Recurrence
			Anatomic	Subjective	
(Elevate=136)			Kaplan-Meier survival curve for recurrence =2.9%		Mesh exposure=1.5%
Rogowski 2015 [13] N=114 (Elevate=62)	Retrospective 18-months	Elevate A	Success: POP-Q ≤1 Mesh=90%	Success: PFDI with no bulge symptoms Mesh=76%	de novo SUI=14.5% de novo OAB=0% Post-op pelvic floor pain=11.3% Post-op dyspareunia=11.3% Mesh exposure=0%
Huang 2015 [14] N=210	Retrospective Median 27 months follow-up	Elevate A	Success: POP-Q ≤1 Anterior Mesh=95% Apical Mesh=94%	UDI-6, IIQ-7 UDI-6 and IIQ-7 scores improved significantly after surgery.	Bladder/bowel injury=0% Internal bleeding=0.5% Pelvic hematoma=1.5% Perineal skin ecchymosis=2.5% Urinary incontinence=24% Urgency=9.5% Urinary retention=1.5% Intermittent voiding=2.5% Constipation=6% Granulation=3.5% Vaginal pain=3% Buttock pain=2% Mesh extrusion=2% (excision=1%) Recurrence=5%
Long 2015 [15] N=141 (Elevate=50)	Prospective 12-months	Elevate A	Surgical failure was defined as the most distal portion of prolapse over stage II or more, regardless of primary or de novo site. Success=94%	UDI-6, IIQ-7 Mesh=Significant improvements from baseline	Bladder injury=0% Rectal injury=0% Blood transfusion=0% UTI=16.7% Voiding dysfunction=2.1% Perineal hematoma=0% Dyspareunia=12% Bladder extrusion=0% Vaginal mesh extrusion=2%
Rapp 2014 [16] N=42	Retrospective 24-months	Elevate A	POP-Q (anterior or apical POP-Q stage 2 or greater associated with an ICIQ-VS domain score of great than 0 for a vaginal bulge): Mesh=Significant improvements in POP-Q points from baseline	ICIQ-VS, ICIQ-FLUTS, IIQ-7 Mesh=Significant improvements from baseline Subjective recurrence in 2 patients	Leg pain=3% Vaginal mesh exposure=5% (excision=2.5%) Urinary retention=13% Anatomical recurrence in 4 patients

9.5 Summary of Efficacy Outcomes in the Literature

Across the selected publications, efficacy outcomes are presented as objective and subjective measures. Objective outcomes (*i.e.*, anatomic outcomes) are presented through POP-Q measurements using various definitions of success or cure. Subjective (*i.e.*, patient-reported) outcomes use a variety of instruments to assess impact on sexual health, incontinence, urogenital distress, vaginal symptoms, and pelvic floor symptoms. Significant objective and subjective improvements from baseline are generally seen in transvaginal surgical mesh cohorts across studies and measures. Furthermore, in studies reporting longer-term outcomes (*i.e.*, greater than

12 months), surgical repair with mesh augmentation is found to result in sustained improvement in efficacy outcomes compared with baseline.

9.6 Summary of Safety Outcomes

All publications reviewed through this literature search provide information on rates of observed mesh exposure or extrusion, and low rates were reported across the studies (range: 0% to 7.3%). The reviewed literature represents a total of 1842 subjects and 43 (2.3%) of subjects were reported to have a mesh exposure or extrusion.

A majority of AEs identified in the studies in the scope for this literature review are known to occur with traditional POP repair. Although not unique to mesh-augmented repair, pelvic pain and de novo dyspareunia have been noted by authors in the general literature as potential device-related events. However, as noted in **Table 9-3**, the rates of these events reported in the reviewed literature are low and appear to be consistent with rates observed in traditional repair.[62] Observed rates of de novo post-operative SUI vary across the reviewed publications (range: 2% to 14.5%), and two studies [5,13] report post-operative SUI rates of 29.8% and 38.1%. Procedures for evaluating the presence of occult or masked SUI are not described in all publications. The rates of de novo or post-operative SUI are consistent with reports following surgical correction of POP and are not necessarily unique to mesh.[63] One study, Marscke et al. (2016) [7], evaluated outcomes in a high-risk patient population consisting of patients with advanced or recurrent prolapse and observed improved anatomical and functional outcomes with no severe adverse events.

Table 9-3: Summary of Adverse Events (AEs) Potentially related to Mesh (All Studies in the Literature Review)

Description	Number of Sites Reporting Event	Range of Reported Rates
Mesh extrusion in vagina	16 (100%)	0 - 7.3%
Pelvic pain	5 (31%)	1 - 11.3%
de novo dyspareunia	5 (31%)	0 - 12%

9.7 Clinical Literature Review Conclusions

Restorelle DirectFix Anterior mesh represents the latest generation of surgical mesh devices designed for POP repair. Coloplast conducted a systematic literature search for publications describing the use of mesh devices that share clinical, technical, and biological characteristics with Restorelle DirectFix Anterior mesh. Our pre-specified search criteria for identifying similar devices were the following mesh characteristics: macroporous, ultra-lightweight, polypropylene (monofilament) mesh utilizing a single-incision transvaginal surgical approach with fixation.

[62] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev 2016;11:CD004014.

[63] Jelovsek JE, Chagin K, Brubaker L et al. A model for predicting the risk of de novo stress urinary incontinence in women undergoing pelvic organ prolapse surgery. *Obstet Gynecol* 2014;123:279–87.

The results of this literature review find high rates of objective and subjective POP improvement for patients treated with transvaginal surgical meshes similar to Restorelle DirectFix Anterior mesh with low rates of adverse events. In published studies evaluating surgical repair of POP using mesh augmentation, extrusion (exposure and/or erosion) into the vagina is the most common reported device-specific event. In this review, low rates of mesh extrusion were reported by all authors (mean across all studies=2.3%).

In its deliberations, the Panel members may find it helpful to consider that this rate of mesh extrusion is significantly lower than rates reported in a 2016 Cochrane Review[64] that focused specifically on anterior POP repair. Coloplast believes that when evaluating publications and meta-analyses, it is important to consider the unique biomechanical properties of ultra-lightweight mesh and the potential impact of changes in medical practice over time. The studies included within the 2016 Cochrane Review represent medical practice from as long as ten years ago. Importantly, the authors of the 2016 Cochrane Review indicate that most of the data informing the review come from medical devices that exited the market in 2012, and many of those devices did not have the ultra-lightweight characteristic of mesh design exhibited by contemporary surgical implants like Restorelle DirectFix Anterior mesh. *All polypropylene mesh studies included in the 2016 Cochrane review were conducted using mesh that is heavier than ultra-lightweight Restorelle DirectFix Anterior mesh; further, the studies included in the 2016 Cochrane Review used a variety of surgical approaches and was not limited to transvaginal procedures*. Moreover, over time, the use of synthetic mesh for POP repair has evolved. The use of surgical mesh for POP repair in the contemporary practice of medicine has been influenced by statements from FDA, global regulatory authorities, and medical societies. Following these guidance recommendations, it is likely that improvements in patient selection, and improved surgical techniques have led to improved outcomes.

In summary, Coloplast believes that the assessment of effectiveness, safety, and benefit/risk needs to be performed in the context of contemporary mesh devices, surgical techniques, and practices.

64 Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev 2016;11:CD004014

Appendix-Section 9

Literature Search Protocol

Coloplast conducted a literature search relevant to Restorelle DirectFix Anterior mesh in PubMed. *See* **Table 9-4**, Search Methodology. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) is an online search engine for biomedical literature that was developed and is maintained by the United States National Center for Biotechnology Information (NCBI) at the United States National Library of Medicine (NLM) located at the United States National Institutes of Health (NIH). It contains over 24 million citations from MEDLINE, life science journals, and online books. MEDLINE is NLM's bibliographic database containing citations and author abstracts from more than 5,600 biomedical journals published in the United States and worldwide dating back to 1946. PubMed was chosen for its large collection of biomedical journal articles and references, as well as its worldwide acceptance for scientific- and medicine-based searches.

Table 9-4: Search Methodology

PubMed	Search Strings: ((pelvic organ prolapse) AND transvaginal) AND anterior) AND mesh ((pelvic organ prolapse) AND (restorelle OR elevate OR uphold)
Filters Applied	• Publication Range: 01 January 2011 through 30 November 2018 • Language: English
Inclusion Criteria	• Full text article available • Human-subject clinical study • Treated condition includes anterior prolapse with/without apical support • Study evaluates the safety and/or performance of Restorelle DirectFix Anterior mesh or a device determined to be similar. Note: Similar devices are defined as monofilament, polypropylene, ultra-lightweight, macroporous mesh using a single-incision transvaginal surgical approach with fixation • Study compares the use of transvaginal synthetic polypropylene mesh to native tissue repair with a minimum of 12 months of follow-up *or* Study provides data from a single-arm cohort with a minimum of 12 months of follow-up
Exclusion Criteria	• Animal study or experimental model • Surgical technique papers • General reviews, letters, responses, editorials, viewpoints, commentaries, white papers • Conference papers, presentations, posters, videos, and abstracts • Not original research or research published elsewhere (*i.e.*, meta-analyses, systematic reviews)

Identification of Similar Devices

Certain technical characteristics of surgical mesh are known to affect the clinical performance and safety of a mesh device for repair of prolapse. Surgical mesh devices considered similar to Restorelle DirectFix Anterior mesh are devices with the following characteristics: Non-absorbable, monofilament, polypropylene, ultra-lightweight,[65] macroporous,[66] and indicated for

[65] Coda A, Lamberti R, Martorana S. Classification of prosthetics used in hernia repair based on weight and biomaterial. *Hernia* 2012;16:9-20. Density classifications: Ultra-light <35 g/m^2, Light ≥35 <70 g/m^2, Standard ≥70 <140 g/m^2, Heavy ≥140 g/m^2.

transvaginal implantation. The criteria included in **Table 9-5** below includes detailed information about each device subject to publication(s) in the literature search and the assessment of similarity for transvaginal medical devices.

Table 9-5: Assessment of Similar Transvaginal Devices for Treatment of POP

Criteria	Restorelle® DirectFix Anterior Mesh (Coloplast)	Elevate™ Anterior and Apical, Prolapse Repair System (Astora Women's Health)	Uphold™ Lite (Boston Scientific)
CLINICAL CHARACTERISTICS			
Intended Use/ Clinical Purpose	*Restorelle DirectFix Anterior Mesh and Restorelle DirectFix Posterior Mesh* are used for tissue reinforcement and stabilization of fascial structures of the pelvic floor in vaginal wall prolapse, where surgical treatment is intended, either as mechanical support or a bridging material for the fascial defect.	*Elevate Anterior & Apical Prolapse Repair System* is a surgical mesh kit intended for transvaginal surgical treatment to correct anterior wall prolapse and vaginal apical prolapse. *Elevate Apical & Posterior Prolapse Repair System* is a surgical mesh kit intended for transvaginal surgical treatment to correct posterior wall prolapse and vaginal apical prolapse.	The *Uphold™ LITE Vaginal Support System* is indicated for tissue reinforcement in women with pelvic organ prolapse, for the transvaginal repair of anterior and apical vaginal wall prolapse.
Indication	Vaginal wall prolapse	Vaginal wall prolapse and vaginal apical prolapse	Anterior vaginal wall prolapse and apical prolapse
Conditions of Use	Single use; controlled clinical setting	Single use; controlled clinical setting	Single use; controlled clinical setting
Site of Application	Pelvic floor	Pelvic floor	Pelvic floor
Surgical Approach	Single-incision Transvaginal	Single-incision Transvaginal	Single-incision Transvaginal
Method of Fixation	Suture	Self-fixating tip	Suture
TECHNICAL CHARACTERISTICS			
Mesh Type	Pre-shaped, non-absorbable, monofilament, polypropylene	Pre-shaped, non-absorbable, monofilament, polypropylene	Pre-shaped, non-absorbable, monofilament, polypropylene
Density	Ultra-lightweight	Ultra-lightweight	Ultra-lightweight
Porosity	Macroporous	Macroporous	Macroporous
BIOLOGICAL CHARACTERISTICS			
Biocompatibility	Permanent synthetic implant; biocompatible	Permanent synthetic implant; biocompatible	Permanent synthetic implant; biocompatible
SUMMARY			
Clinical	Subject Device	Similar	Similar
Technical	Subject Device	Similar	Similar
Biological	Subject Device	Similar	Similar

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10. CONSIDERATIONS: APPROPRIATE PATIENT POPULATION

10.1 Focus of this Section

In the Federal Register notice regarding this Panel meeting,[67] FDA announced that one purpose is to seek the Panel's scientific and clinical input regarding "the appropriate patient population," regarding surgical mesh used in transvaginal treatment of anterior POP.

This section is provided to present the current opinions of United States medical societies that may be informative as the Panel considers how to advise the FDA regarding the appropriate patient population for the use of surgical mesh placed transvaginally to treat anterior POP. Coloplast conducted a literature search to identify clinical practice guidelines, position statements, or recommendations published by United States specialty medical societies relevant to the consideration of the appropriate patient population for anterior POP repair using transvaginal synthetic mesh with or without apical support. The following are statements from United States specialty societies that have issued recent opinions pertinent to this topic. *See* **Appendix-Section 10** at the end of this section for the search protocol.

10.2 Considerations – Opinions of Medical Societies

10.2.1 Opinion of the American College of Obstetricians and Gynecologists (ACOG)/Association of Urogynecologic Surgeons (AUGS) – Practice Bulletin Number 185, November 2017[68]

The 2017 ACOG/AUGS practice bulletin makes the following statement specific to the selection of the patient population for surgical treatment of POP with vaginal mesh repair:

> [POP] vaginal mesh repair should be limited to high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior or apical compartments) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures. Before placement of synthetic mesh grafts in the anterior vaginal wall, patients should provide their informed consent after reviewing the benefits and risks of the procedure and discussing alternative repairs.
> (Level C evidence – consensus and expert opinion)

10.2.2 Opinion of the American Urogynecologic Society AUGS Best Practice Statement: Evaluation and Counseling of Patients with POP[69]

The 2017 AUGS best practice statement makes the following recommendation:

> Women with prolapse should have an examination to quantify the loss of anatomic support and should be evaluated for associated bladder, bowel and prolapse symptoms, as well as associated bother. Treatment options should be

[67] Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments, 83 Fed. Reg. 63,516 (Dec. 10, 2018).

[68] Committee on Practice Bulletins-Gynecology, American Urogynecologic Society. Practice Bulletin No. 185: Pelvic Organ Prolapse. *Obstet Gynecol* 2017;130:e234-e250.

tailored to meet the patient's medical health and personal functional goals. In most cases, women should be informed of the range of treatment options including observation as well as nonsurgical and surgical management.

The 2017 practice statement also provides recommendations regarding counseling the population of asymptomatic women with POP:

- "Asymptomatic women without evidence of urinary retention can be offered expectant management."

- "Asymptomatic women should be offered an appropriate range of interventions based upon their medical histories and treatment goals, including vaginal pessary and surgery."

10.3 Considerations – Contemporary Choices by Surgeons with Patients

These contemporary recommendations by medical societies pertinent to selection of the appropriate population for anterior POP repair with or without apical repair represent surgeons' opinions and reflect the evolving patterns in the use of surgical mesh for anterior POP repair, including the use of Restorelle DirectFix Anterior mesh. In general, these statements represent contemporary practice in the United States that surgical repair of anterior POP with surgical mesh is often reserved for: (1) symptomatic, higher-risk women, such as those with recurrent anterior prolapse with or without apical prolapse after prior pelvic surgery, and (2) patients with co-morbidities that an experienced surgeon deems may increase the need for additional mechanical support during the repair and long-term healing process.

Our observations of subject characteristics in the Restorelle 522 Study—a real-world post-market two cohort clinical study—corroborate these impressions. As described in this document in Sections 6 and 7, the protocol for the study called for choice of treatment arm after consultation and discussion between the surgeon and each individual subject to determine if the subject would participate in the native tissue repair cohort or the mesh cohort. Subjects were not randomized. Although many characteristics of the subjects in each cohort were similar, the subjects who joined the mesh cohort were more likely to have a history of prior pelvic reconstructive surgery and clinical features that may impair tissue repair and increase the need for structural reinforcement with mesh.

10.4 Key Take-Aways

- As the Panel thinks about the factors that FDA should consider regarding the patient population, Panel members may wish to keep in mind that it is important for patients with anterior POP requiring surgical repair to have options based on their individual medical history, condition and goals.

- A surgeon counseling and patient consent process between each patient and her surgeon is valuable in choosing the treatment for anterior POP.

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[69] AUGS Best Practice Statement: Evaluation and Counseling of Patients with Pelvic Organ Prolapse. *Female Pelvic Med Reconstr Surg* 2018;24:256.

- A major factor that contributes to the evaluation of efficacy, safety, and the benefit/risk profile of all medical devices is the intended use and indication that will be stated in the approved labeling, which includes the intended population.

Appendix-Section 10

Search Protocol for Medical Society Guidelines, Position Statements, or Recommendations

Coloplast conducted a search in both PubMed and medical society websites to identify clinical practice guidelines, position statements, or recommendations published by specialty medical societies relevant to the use of transvaginal synthetic mesh for repair of anterior POP with or without apical support. *See* **Table 10-1**.

Table 10-1: Search Methodology

Publication type	Clinical practice Guidelines, Position Statements, or Recommendations from specialty medical societies
Population	Female patients with POP
Subject	Repair of the anterior vaginal compartment prolapse using synthetic mesh with/without apical support
Methodology	Searches were performed in PubMed and specialty society websites (see search detail below). Conclusions and recommendations from the guidelines and statements are provided below if they contain information concerning transvaginal repair of anterior and/or apical compartment prolapse using synthetic mesh
Language	Non-English-language articles were excluded
Search Detail	PubMed Search String: (“practice guideline” [All Fields] OR “statement” [All Fields] OR “position statement” [All Fields]) AND ("pelvic organ prolapse" OR "POP"[All Fields]) Date Filter: 2011/01/01 to 2018/11/30 Websites Searched: Specialty medical societies: AAGL, ACOG, AFU, AUGS, BSUG, CUA, EAU, EUGA, IUGA, RCOG, SAUGA, SGS, SUFU, SOGC

11. CONSIDERATIONS: SURGEON EDUCATION AND TRAINING

11.1 Focus of this Section

Surgical expertise can impact the safety, efficacy, and benefit/risk profile of a medical device for its intended population. In the Federal Register notice regarding this Panel meeting,[70] FDA announced that one purpose is to seek the Panel's scientific and clinical input regarding "the physician training needed for these devices," regarding surgical mesh placed transvaginally in the anterior vaginal compartment to treat POP.

This section is provided to present the current opinions of United States medical societies that may be informative as the Panel considers how to advise FDA regarding surgeon education and training related to the use of surgical mesh placed transvaginally to treat anterior POP. Coloplast conducted a literature search to identify clinical practice guidelines, position statements, or recommendations published by United States specialty medical societies that provide recommendations regarding surgeon training for use of transvaginal synthetic mesh for anterior POP repair with or without apical support. *See* **Appendix-Section 11** at the end of this section for the search protocol.

11.2 Opinions of Medical Societies

11.2.1 Opinion of the American College of Obstetricians and Gynecologists (ACOG)/Association of Urogynecologic Surgeons (AUGS) – Practice Bulletin Number 185, November 2017[71]

The 2017 ACOG/AUGS practice bulletin makes the following statement specific to surgeon training for surgical treatment of POP with vaginal mesh repair:

> Surgeons who perform POP surgery with biologic grafts or synthetic mesh grafts should have training specifically for these procedures and should be able to counsel patients regarding the risk-benefit ratio for the use of mesh compared with native tissue repair.
> (Level C evidence – consensus and expert opinion)

[70] Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments, 83 Fed. Reg. 63,516 (Dec. 10, 2018).

[71] Committee on Practice Bulletins-Gynecology, American Urogynecologic Society. Practice Bulletin No. 185: Pelvic Organ Prolapse. *Obstet Gynecol* 2017;130:e234-e250.

11.2.2 The American College of Obstetricians and Gynecologists (ACOG)/Association of Urogynecologic Surgeons (AUGS) Committee Opinion No. 694 Summary: Management of Mesh and Graft Complications in Gynecologic Surgery[72]

The 2017 ACOG/AUGS committee opinion makes the following statement specific to surgeon training and experience regarding management of mesh and graft complications in gynecologic surgery:

> Pelvic pain (including dyspareunia), possibly related to nonexposed mesh, is complex, may not respond to mesh removal, and should prompt referral to a clinician with appropriate training and experience, such as a female pelvic medicine and reconstructive surgery specialist.

11.2.3 Opinion of the American Urogynecologic Society (AUGS) Best Practice Statement: Evaluation and Counseling of Patients with Pelvic Organ Prolapse[73]

The 2017 AUGS best practice statement makes the following recommendation, from which it can be inferred that surgeon training should be appropriate to ensure competency in each of these activities related to the evaluation, diagnosis and counseling of patients presenting with POP.

> For patients presenting with POP:
>
> 1. Determine the duration and severity of pelvic symptoms and associated bother.
> 2. Ask specifically about urinary, bowel, sexual symptoms, and previous treatments.
> 3. Obtain a medical and surgical history including previous pelvic surgery.
> 4. Perform a physical examination including a POP-Q examination and assessment of pelvic floor muscle function.
> 5. Quantify the extent of the prolapse using the POP-Q examination and confirm that the examination findings reflect the patient's experience.
> 6. Assess for abnormal vaginal bleeding.
>   a. Document the Patient’s denial of vaginal bleeding.
>   b. Evaluate symptoms of vaginal bleeding to rule out premalignant or malignant conditions.

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[72] Committee Opinion No. 694 Summary: Management of Mesh and Graft Complications in Gynecologic Surgery. *Obstet Gynecol* 2017;129:773-4.

[73] AUGS Best Practice Statement: Evaluation and Counseling of Patients with Pelvic Organ Prolapse. *Female Pelvic Med Reconstr Surg* 2018;24:256.

7. Assess bladder function.

    a. Continence: Consider cough stress test with the prolapse in the native, neutral, and reduced position (at bladder volume of 300 mL or capacity, whichever is less). If considering surgery, assess risk of occult stress urinary incontinence using available risk prediction models.

    b. Emptying: Evaluate PVR urine volume in patients with anterior vaginal wall prolapse beyond the hymen or abnormal voiding symptoms.

8. Asymptomatic women without evidence of urinary retention can be offered expectant management.

9. Asymptomatic women should be offered an appropriate range of interventions based upon their medical histories and treatment goals, including vaginal pessary and surgery.

11.3 Summary – Contemporary Surgeon Education and Training

In general, in contemporary practice in the United States, surgical repair of anterior POP with mesh is increasingly performed by surgeons who specialize in pelvic reconstructive surgery and have specific education and experience in the use of surgical mesh for anterior POP repair as well as the management of potential complications of prior surgery. Coloplast believes that in contemporary practice, surgical repair of anterior POP with mesh is also increasingly performed by surgeons who are trained and experienced in the evaluation of patients with SUI urinary incontinence, and who are skilled in the provision of patient-specific counseling regarding the options for management and the potential risk-benefit profile of each of the management options.

Coloplast facilitates educational opportunities for surgeons related to the use of its medical devices. The options for education allow the surgeon to take into account her or his individual prior training, experience, and level of knowledge regarding transvaginal anterior POP surgical procedures.

Appendix – Section 11

Search Protocol for Medical Society Guidelines, Position Statements, or Recommendations

Coloplast conducted a search in both PubMed and medical society websites to identify clinical practice guidelines, position statements, or recommendations published by specialty medical societies relevant to the use of transvaginal synthetic mesh for repair of anterior compartment prolapse with/without apical support. *See* **Table 11-1**.

Table 11-1: Search Methodology

Publication type	Clinical practice Guidelines, Position Statements, or Recommendations from specialty medical societies
Population	Female patients with POP
Subject	Repair of the anterior vaginal compartment prolapse using synthetic mesh with/without apical support
Methodology	Searches were performed in PubMed and specialty society websites (see search detail below). Conclusions and recommendations from the guidelines and statements are provided below if they contain information concerning transvaginal repair of anterior and/or apical compartment prolapse using synthetic mesh
Language	Non-English-language articles were excluded
Search Detail	PubMed Search String: (“practice guideline” [All Fields] OR “statement” [All Fields] OR “position statement” [All Fields]) AND ("pelvic organ prolapse" OR "POP"[All Fields]) Date Filter: 2011/01/01 to 2018/11/30 Websites Searched: Specialty medical societies: AAGL, ACOG, AFU, AUGS, BSUG, CUA, EAU, EUGA, IUGA, RCOG, SAUGA, SGS, SUFU, SOGC

12. CONCLUSION: KEY FACTORS FOR PANEL TO CONSIDER REGARDING THE ASSESSMENT OF THE EFFECTIVENESS, SAFETY, AND BENEFIT/RISK OF "MESH PLACED TRANSVAGINALLY IN THE ANTERIOR VAGINAL COMPARTMENT"

POP can significantly impact a woman's health by causing impaired urinary, defecatory, and sexual function; significant discomfort; inconvenience; and a diminished quality of life. Although there are non-surgical, conservative treatment options, for many women these options fail to provide adequate symptom relief. For those patients, surgical procedures are typically the most appropriate option. Given the variability in women's treatment goals, medical history, co-morbidities, and anatomy, it is critically important that there be a variety of surgical treatment options available. Transvaginally implanted surgical mesh for the repair of anterior POP is one of those currently available treatment options, and Coloplast believes it is important for women's health that it remain an available option.

To that end, Coloplast appreciates the Panel's thoughtful consideration of the factors that FDA may want to consider when assessing the effectiveness, safety, and benefit/risk profile of surgical mesh intended for transvaginal repair of anterior POP and also when recommending potential patient populations or surgeon training. To assist in this important task, Coloplast respectfully suggests the following factors for the Panel's consideration and discussion.

12.1 Design Characteristics of Surgical Mesh Devices

As described in Section 4 of this document, not all surgical meshes are alike in their design features. Restorelle's design characteristics have been shown to be associated with better outcomes, including better host tissue response and in-growth and reduced risks of inflammation and infection. Thus, when making its recommendations to FDA regarding factors to use in assessing the benefits and risks of surgical meshes for transvaginal anterior POP repair, the Panel may wish to consider the following design elements of surgical mesh devices and how those elements may contribute to the benefits or risks associated with a device:

- Device material: what are the biocompatibility and toxicity characteristics of the material?
- Porosity: is the mesh pore size sufficiently large (*e.g.*, Type 1 macroporous) to allow for neovascularization, cell migration, and access for microphages to eliminate bacteria?
- Density: is the mesh's density light enough (*e.g.*, ultra-lightweight) to elicit an improved host tissue response?
- Flexibility and conformity: does the device's design minimize factors that could lead to undesired effects?
- Thickness: how does the mesh's thickness affect tissue in-growth?

12.2 Design of the Clinical Studies Supporting PMAs

The Panel may wish to consider how the clinical study design of the 522 studies used to support PMAs for implantable medical devices for transvaginal anterior POP repair may reveal important insights about the way the medical devices are currently used in real-world practice and should be used in the future.

As described in Section 6, the Restorelle 522 Study differs from many traditional PMA clinical trials in that it is a post-market, real-world study that relied on consultation and discussion between patients and surgeons to choose patients' assignment to treatment arms. The benefit of such a clinical study design is that it provides insights into the contemporary decisions surgeons are making about whether a patient is a good candidate for transvaginal anterior POP repair with surgical mesh versus native tissue repair. The baseline patient characteristics of the Restorelle 522 Study presented in Section 7 may be interpreted to reveal some of the factors that appear to be influencing contemporary real-world surgical decisions about transvaginal surgical treatment options for anterior POP repair.

Therefore, when making recommendations to FDA regarding the Agency's review and consideration of factors it should consider regarding the clinical studies supporting pending PMAs for surgical mesh devices intended for the transvaginal repair of anterior POP, the Panel may wish to identify the features of the clinical study design that the Panel believes are particularly important when assessing the safety, efficacy, and benefit/risk profile of the devices under review.

12.3 Use History and Associated Surveillance Data

As described in Section 5, surgical mesh devices intended for transvaginal repair of anterior POP have been cleared by FDA for over a decade, providing a body of safety and efficacy information that is not often available for new investigational devices undergoing PMA review. As described in Section 8, FDA's MDR requirements mean that the public and the Agency both have access to information about the postmarket, real-world safety profile of surgical mesh devices intended for transvaginal repair of anterior POP. In addition, as summarized in Section 9, the devices' long use history also means that published literature on the safety and effectiveness of these devices is also publicly available.

The long regulatory and use history may be beneficial to FDA when considering the factors to use for assessing the safety, efficacy, and benefit/risk profile of these devices. The significant real-world experience eliminates some of the uncertainty that FDA typically faces when assessing the benefit/risk profile of a new PMA-pending device that can only rely on clinical trial data to support its PMA. Data from randomized, controlled clinical trials, though very beneficial, has its limitations when assessing real-world benefit and risk because of the restrictions placed on patient populations and surgeon practices, dictated by clinical trial protocols and the need to control as many variables as possible. Real-world data, such as data from MDR reports and literature reviews, on the other hand, takes into account the full spectrum of patient and surgeon experience.

Thus, the Panel may wish to consider in its recommendations to FDA how the Agency should weigh the importance of postmarket safety and efficacy data from MDR reports and literature reviews when assessing the devices' safety, efficacy, and overall benefit/risk profile.

12.4 Appropriate Patient Populations

FDA has tasked the Panel with providing recommendations regarding the appropriate patient population for treatment of anterior POP with transvaginal surgical mesh. Coloplast defers to the Panel's judgment as how to define the recommended patient population and respectfully suggests that the Panel consider the following when making its recommendations:

- Opinions of medical societies active in the treatment of POP, including, but not limited to, the American College of Obstetricians and Gynecologists and the Association of Urogynecologic Surgeons.

- Contemporary practice regarding patient selection for treatment with transvaginal mesh for anterior POP repair, rather than native tissue repair or other alternate therapies. Sources for identification of contemporary practice may include: medical society opinions; the baseline clinical characteristics of patients assigned to the mesh and NTR treatment arms of the 522 studies; observations in the literature; and the Panel members' own practices and those of their colleagues.

- The benefits of a surgeon counseling and patient consent process between the patient and her surgeon when selecting treatment options.

- The importance of ensuring a variety of treatment options remain available on the market for women, so that there are sufficient choices available to find an option that is appropriate given a patient's clinical history, co-morbidities, anatomy, and personal preference.

12.5 Appropriate Surgeon Education and Training

FDA has also tasked the Panel with providing recommendations regarding the training of surgeons who implant transvaginal surgical mesh for anterior POP repair. Coloplast believes that proper surgical skill and expertise can reduce the occurrence and severity of potential clinical risks associated with anterior POP repair with transvaginal surgical mesh. Surgeons with the necessary knowledge and skills regarding patient selection, surgical device placement, and identification and management of adverse events maximize beneficial patient outcomes. Again, Coloplast defers to the Panel's judgement as how to define its recommendations regarding training, but respectfully suggest that the Panel consider the following:

- Opinions of medical societies active in the treatment of POP, including, but not limited to, the American College of Obstetricians and Gynecologists and the Association of Urogynecologic Surgeons.

- The amount and format of training needed to ensure surgeons have the necessary knowledge and skills to minimize risk and maximize successful patient outcomes.

- Contemporary practice with respect to the skills and requisite knowledge and experience for surgeons implanting transvaginal surgical mesh for treatment of anterior POP. Sources for identification of contemporary practice may include: medical society opinions; observations in the literature; and the Panel members' own practices and those of their colleagues.

* * * * *

As stated at the outset, Coloplast appreciates the opportunity to present its position, postmarket experiences, and views to the Panel. Coloplast hopes that the information presented in this document will be helpful for the Panel as it identifies the factors that FDA should consider when evaluating the efficacy, safety, and benefit/risk profile of transvaginal surgical mesh for anterior POP repair, as well as the appropriate patient population and surgeon training. Coloplast looks forward to the opportunity to discuss the elements of this briefing document with the Panel members at the upcoming Panel Meeting.